UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

Neurochemical systems involved in the formation of placebo effects in pain and Major Depression

Jon-Kar Zubieta, M.D., Ph.D.

William H. and Edna Stimson Presidential Endowed Chair

Professor and Chair

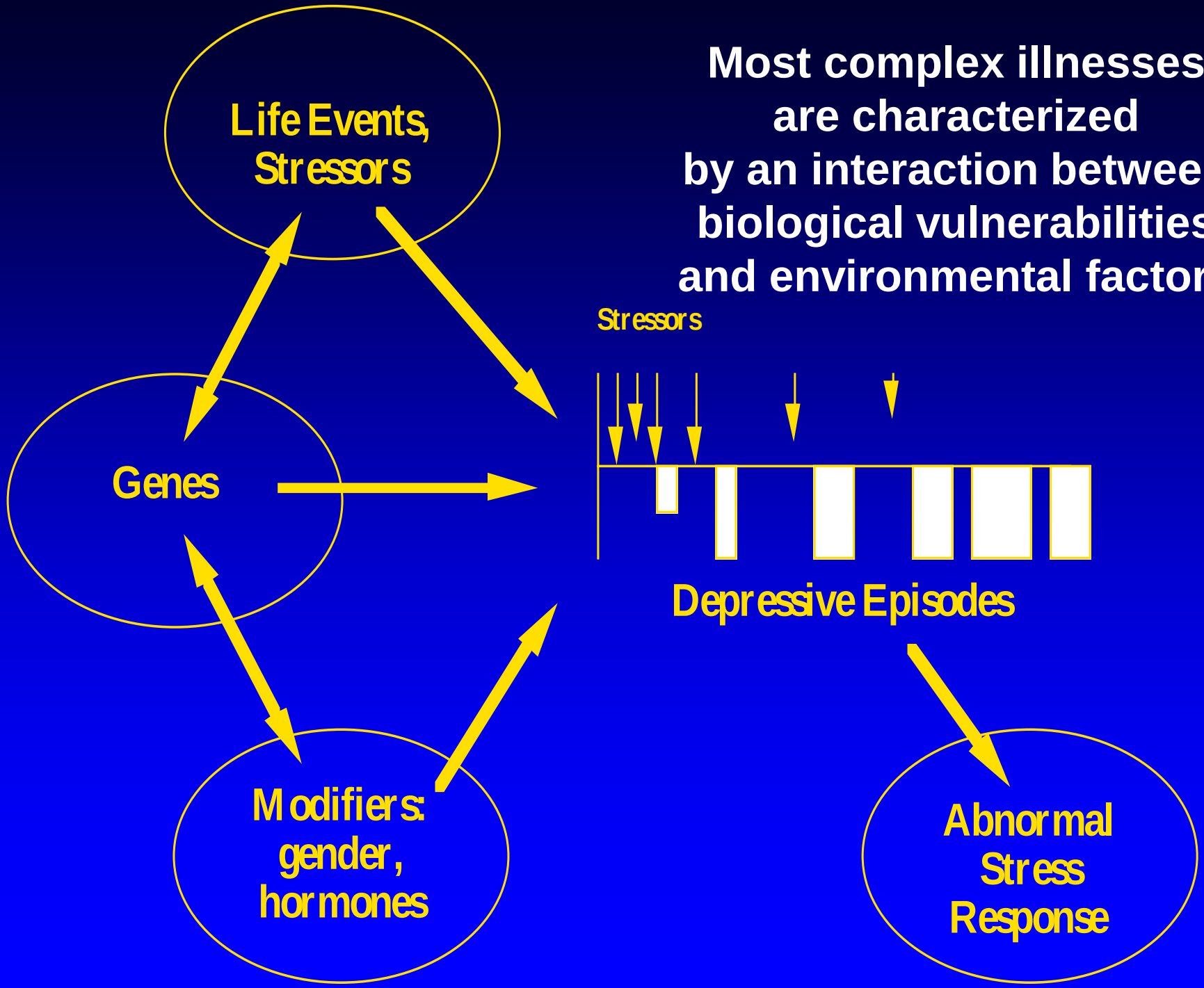
Department of Psychiatry

Psychiatrist-in-Chief

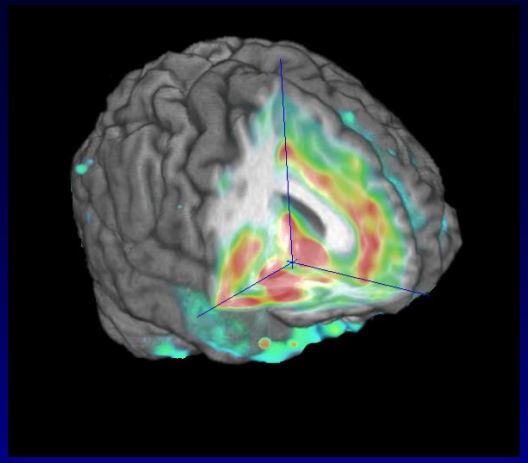
University Neuropsychiatric Institute

No Disclosures

Most complex illnesses are characterized by an interaction between biological vulnerabilities and environmental factors



Mu Opioid Neurotransmission

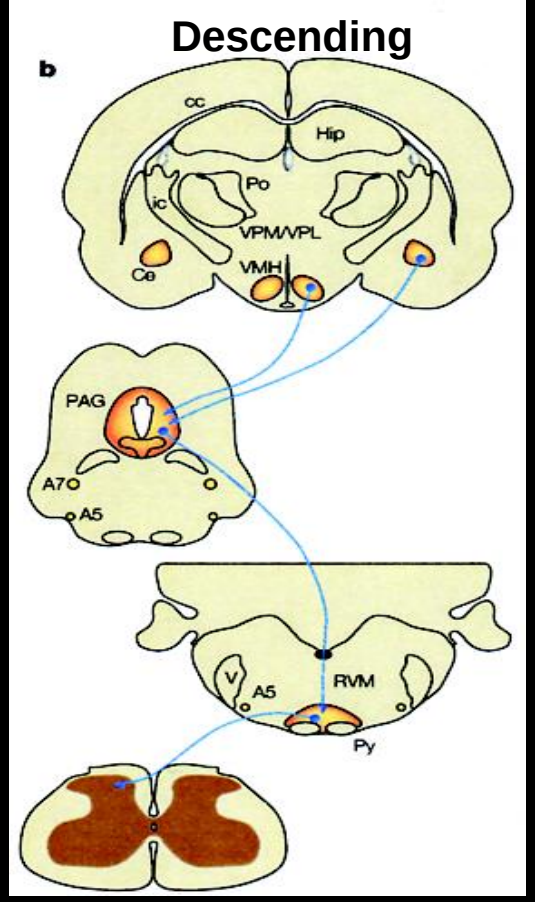


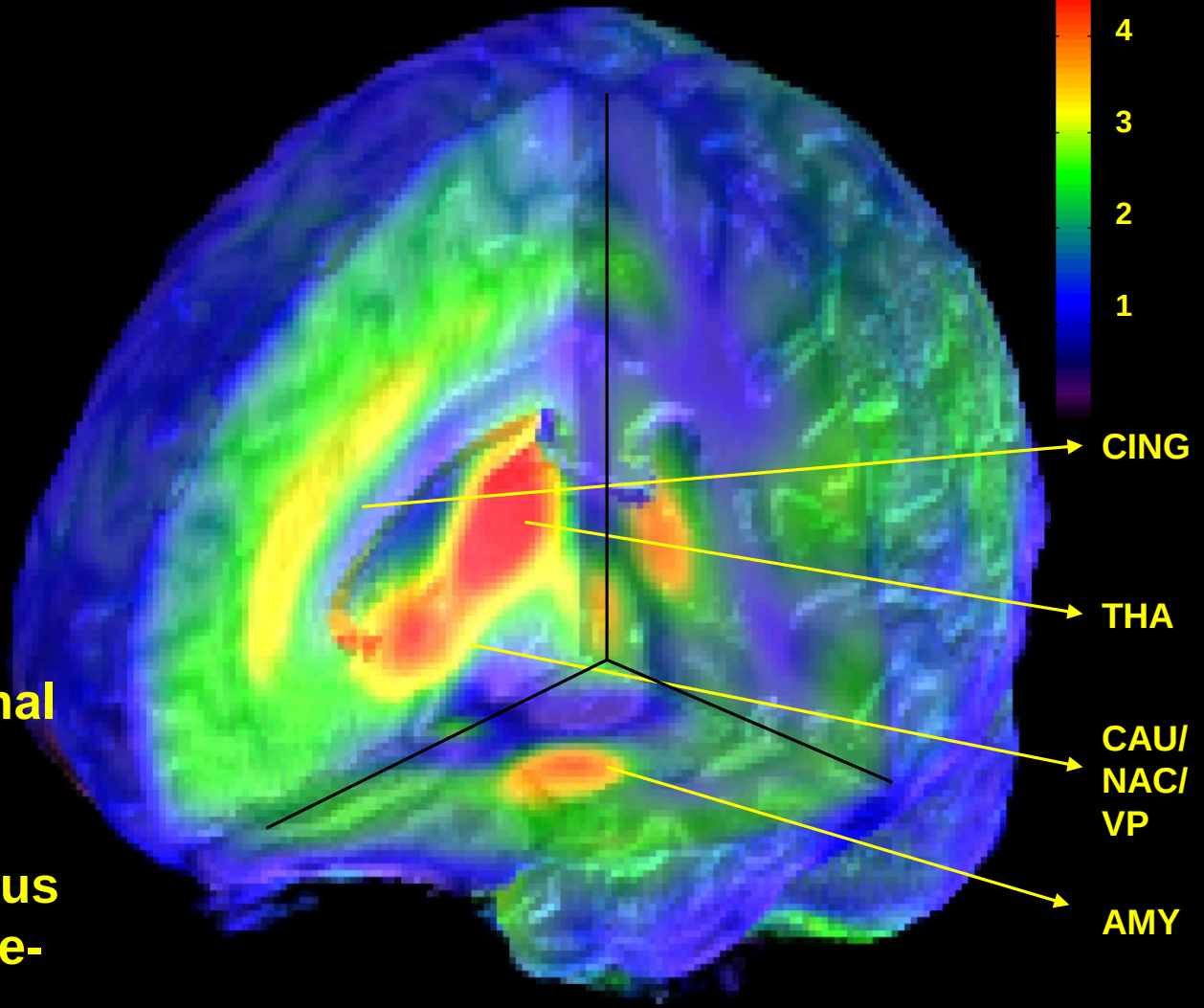
- Experimental evidence (animal models and humans) and transgenic models implicate them in:
  - Endogenous opioid analgesia and effects of opiate analgesics
  - Stress responses and stress-induced analgesia
  - Regulation of affiliative, social behavior
  - Regulation of responses to salient and appetitive stimuli, including food and drugs of abuse
  - Thought to mediate placebo effects during expectation of analgesia

- Direction of modulation is typically suppressive of the relevant response (e.g., pain, stress, anxiety, …)
- Typically activated by stimuli that threatens the homeostasis of the organism (e.g., unpredictable stress, sustained, more rostral pain…)

CNS Inhibitory Controls

Mu Opioid Receptor-Mediated Neurotransmission





Distributed in pain regions but also "affective / motivational circuits" - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

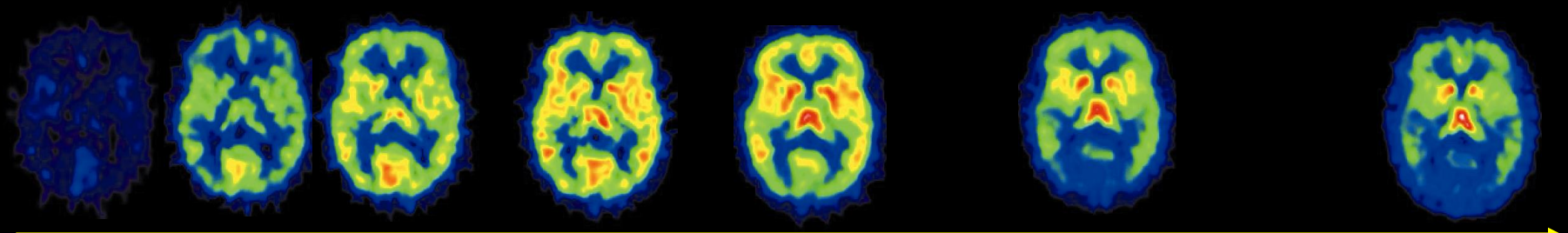
Receptor Quantification with PET

Tracer Transport

(rCBF x Tracer Extraction)

Incorporation to

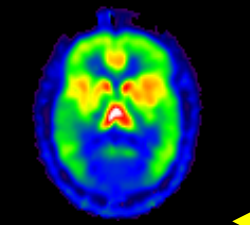
Specific Binding Sites

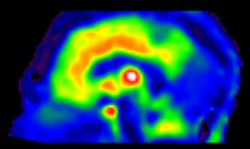


Data Analysis

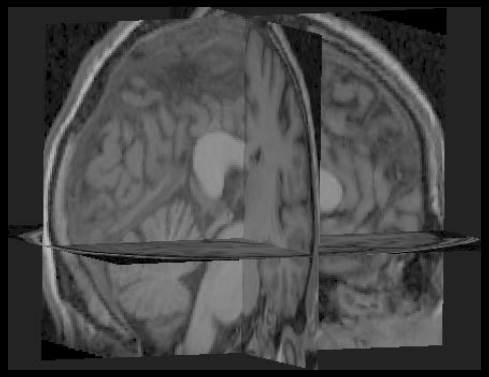
Generation of Parametric Maps

e.g., Logan Plots (K_1, DVR)





Coregistration with Anatomical MRI

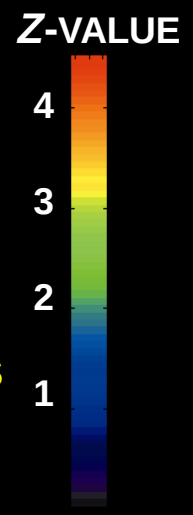


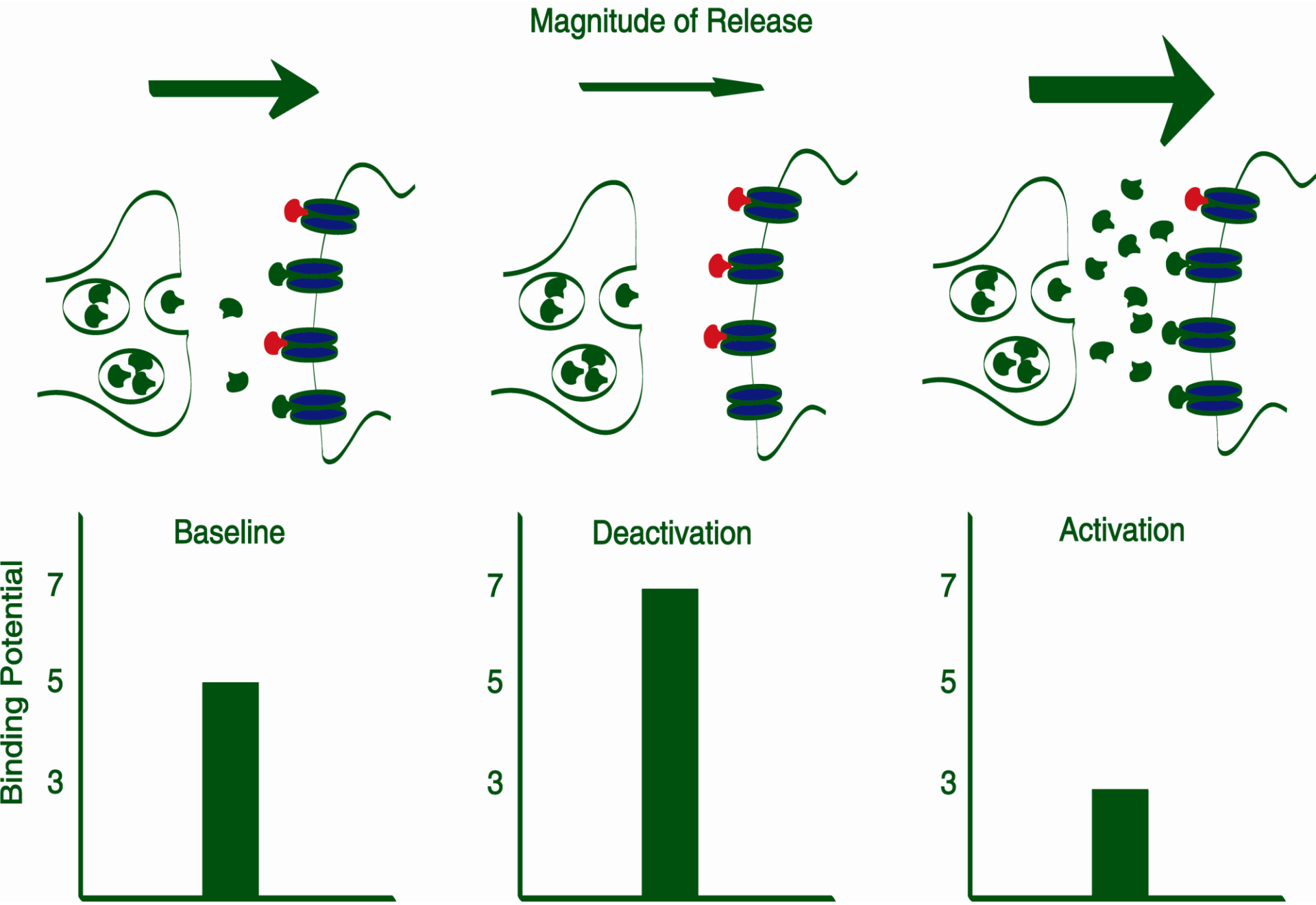
Non-Linear Anatomical Standardization

(ICBM Coordinates)

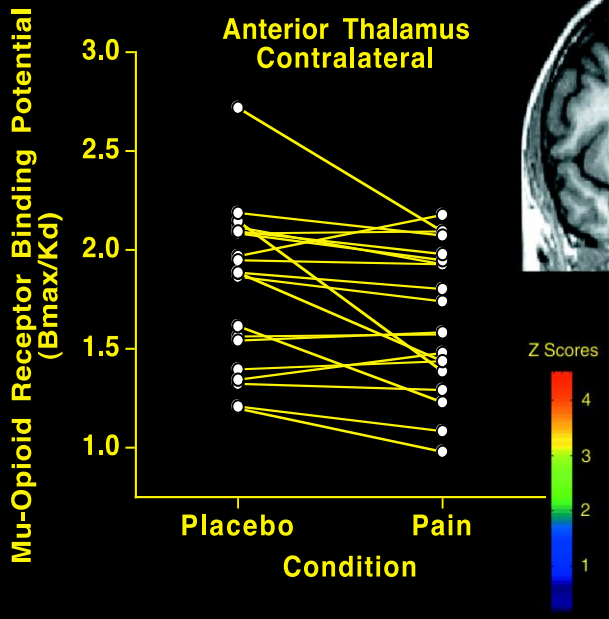
STATISTICAL PARAMETRIC MAPS OF SIGNIFICANCE

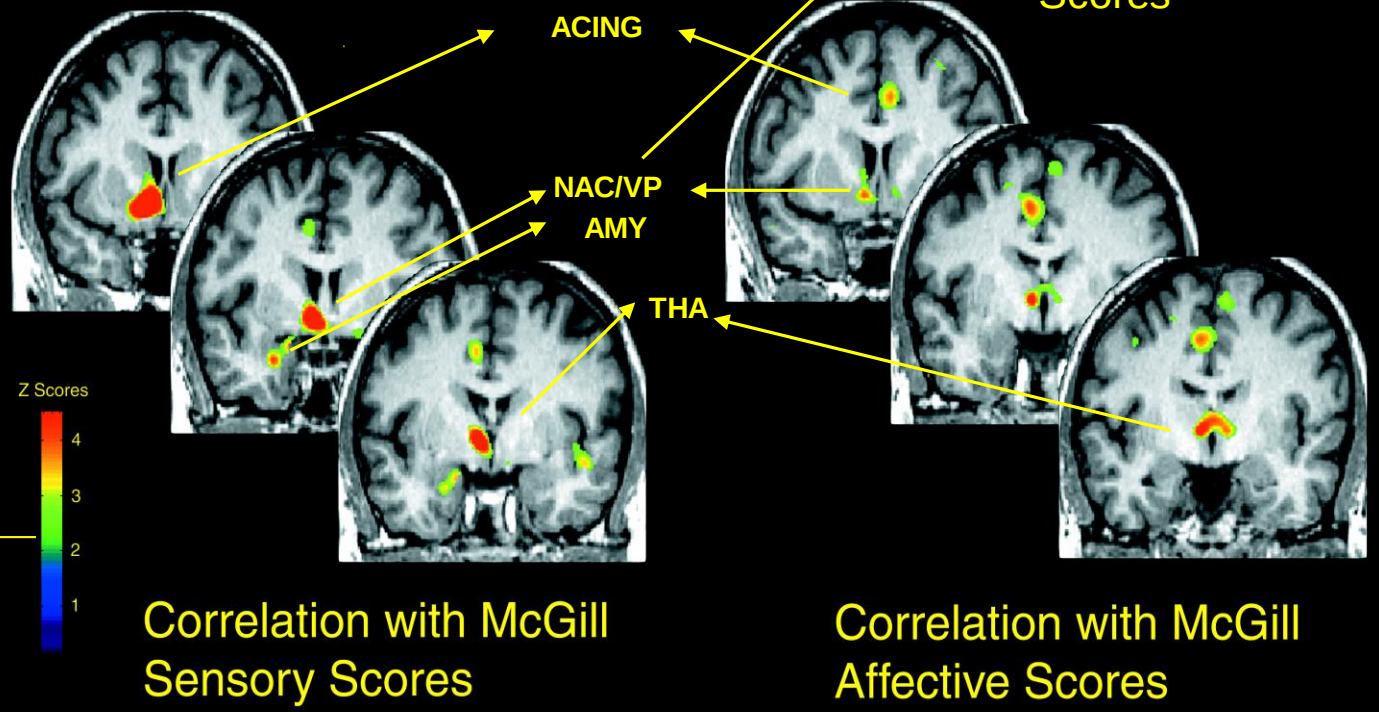
(SPM)




Magnitude of Release
Baseline
Deactivation
Activation
Binding Potential
7
5
3
7
5
3
7
5
3

Endogenous Opioid Regulation of the Pain-Stress Experience





Correlation with PANAS Negative Affect Scores

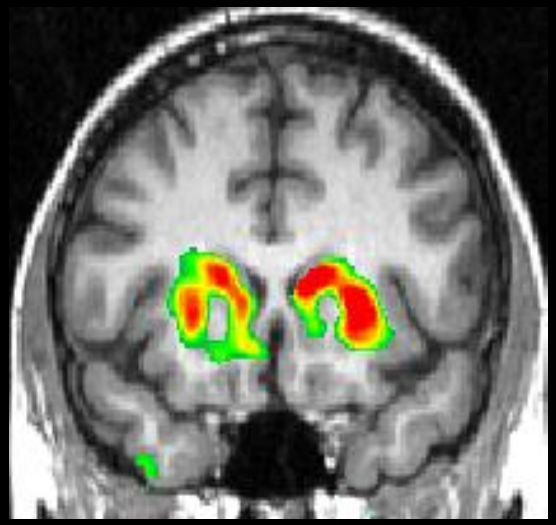
Correlation with McGill Sensory Scores

Correlation with McGill Affective Scores

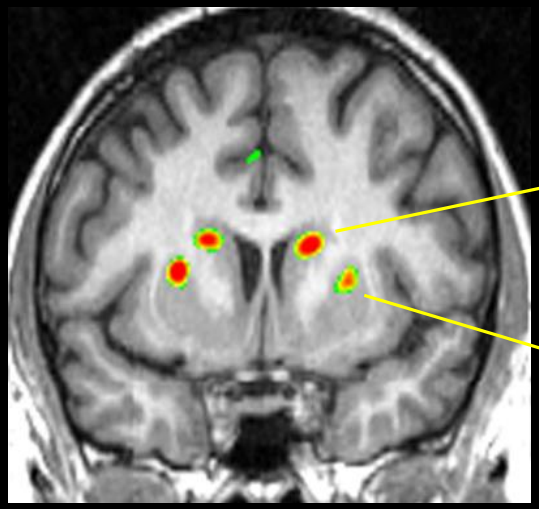
(Zubieta et al., Science 293:311, 2001)

Pain-Induced Activation of DA D2/3 Neurotransmission

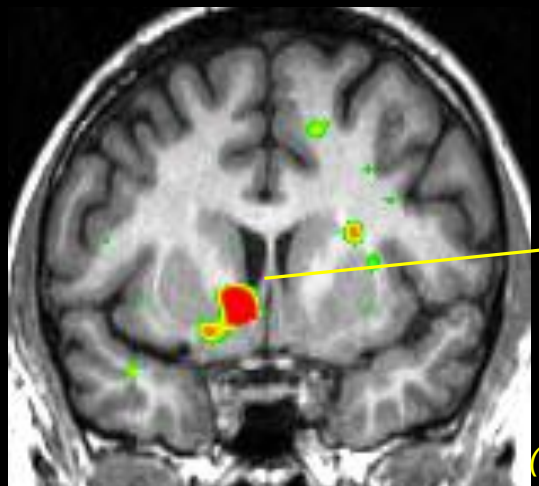
Overall Response: Baseline - Pain



Saline Control - Pain



(Baseline - Pain) - (Saline Control - Pain)

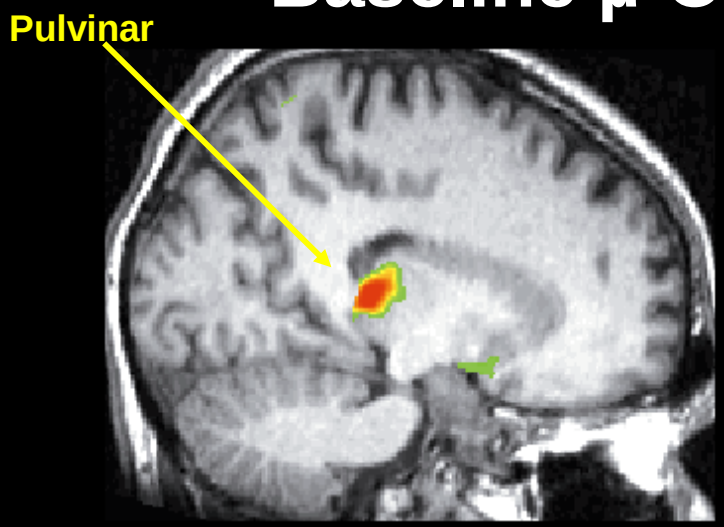


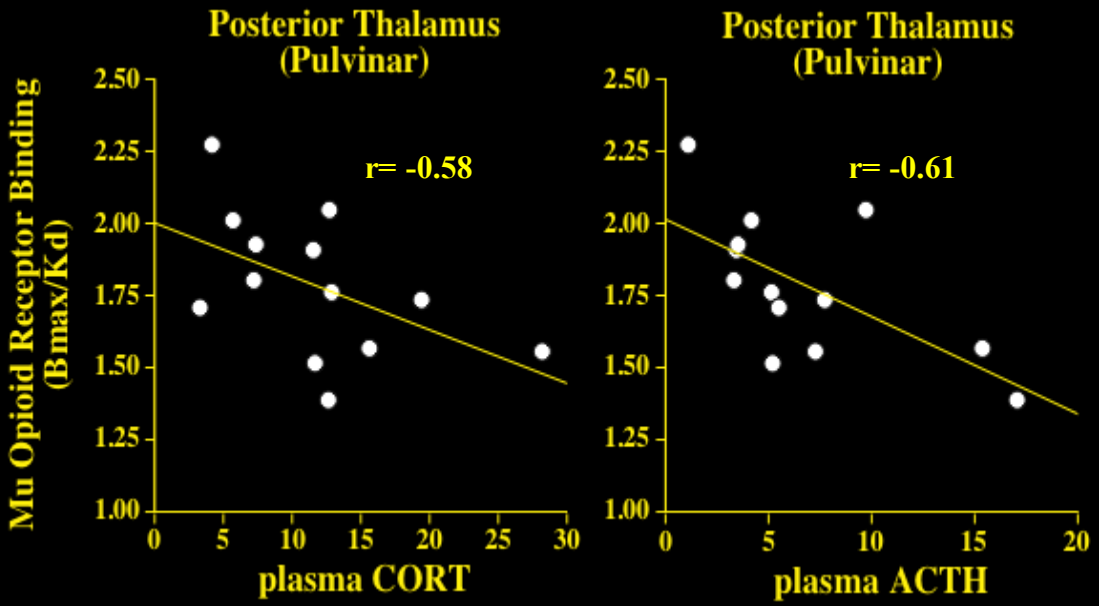
Correlations

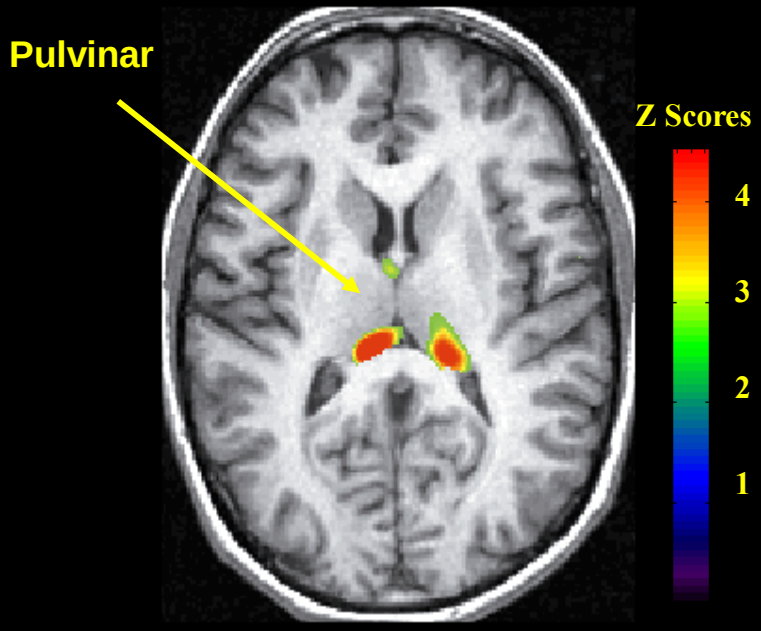
- MPQ Sensory, r = 0.67
- VAS Intensity, r = 0.72
- MPQ Sensory, r = 0.76
- VAS Intensity, r = 0.79
- PANAS negative, r = 0.53
- PANAS fear, r = 0.45

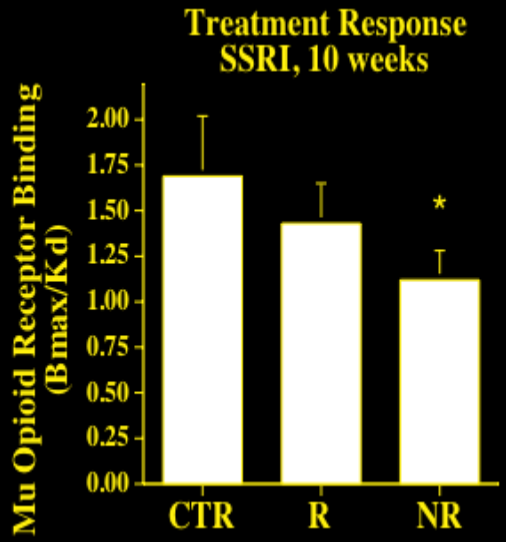
(Scott et al., J Neuroscience, 2006)

Major Depression *vs.* Control Women
Baseline μ-Opioid Receptor Binding





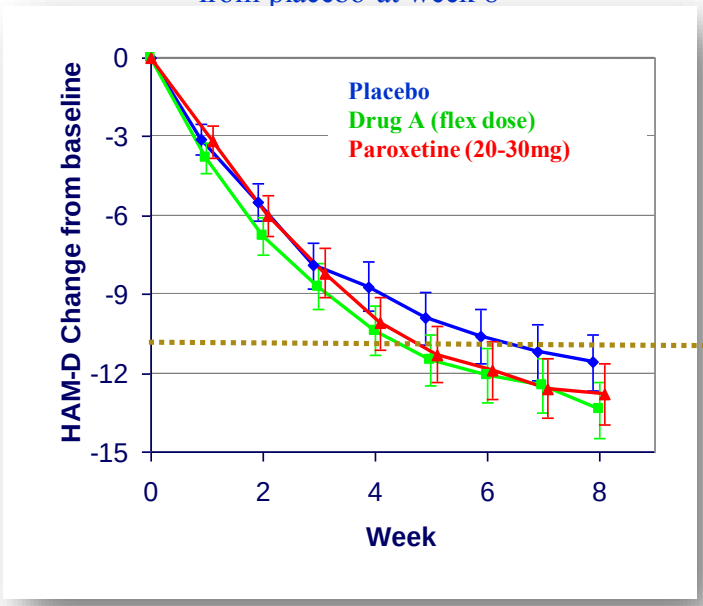




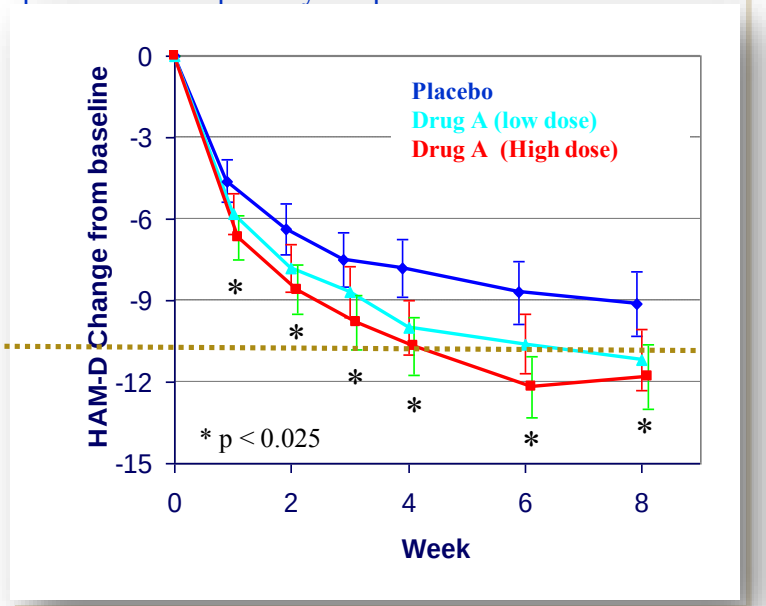
Kennedy et al., Arch Gen Psychiatry, 2006

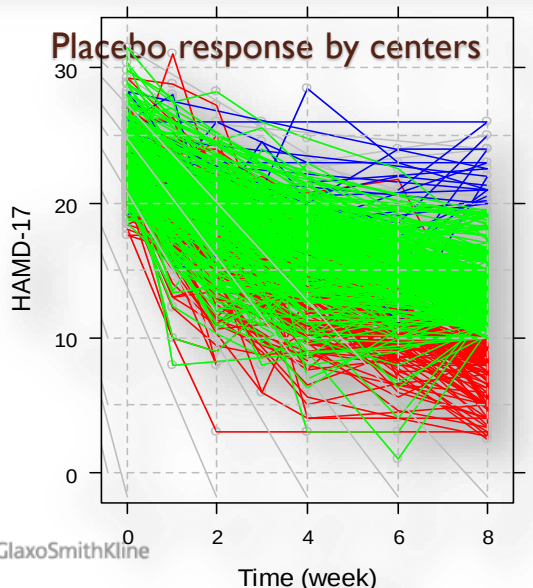
Placebo Response and Study Outcomes

Drug A (flex dose) and Paroxetine did not separate from placebo at week 8

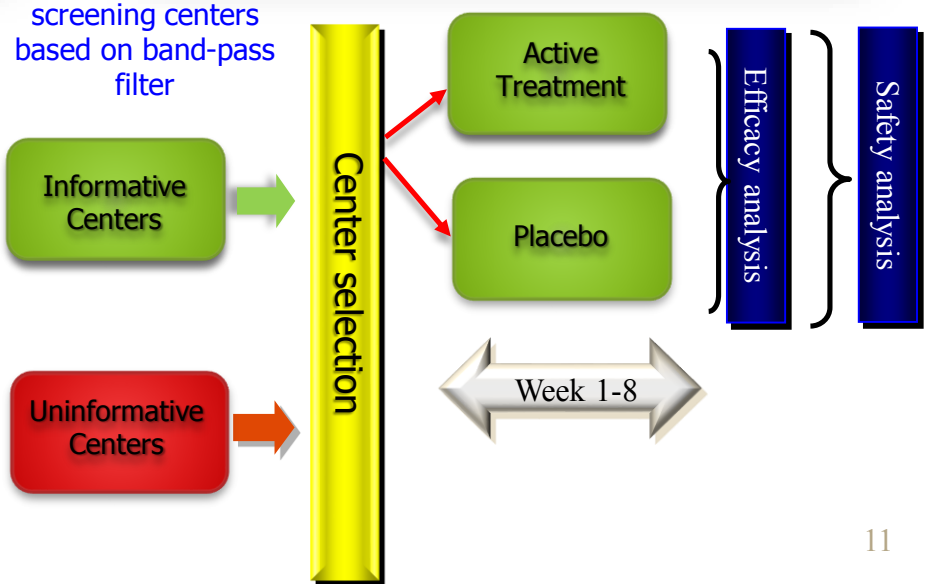


Drug A (highest dose) statistically separates from placebo on the primary endpoint from week 1 onwards





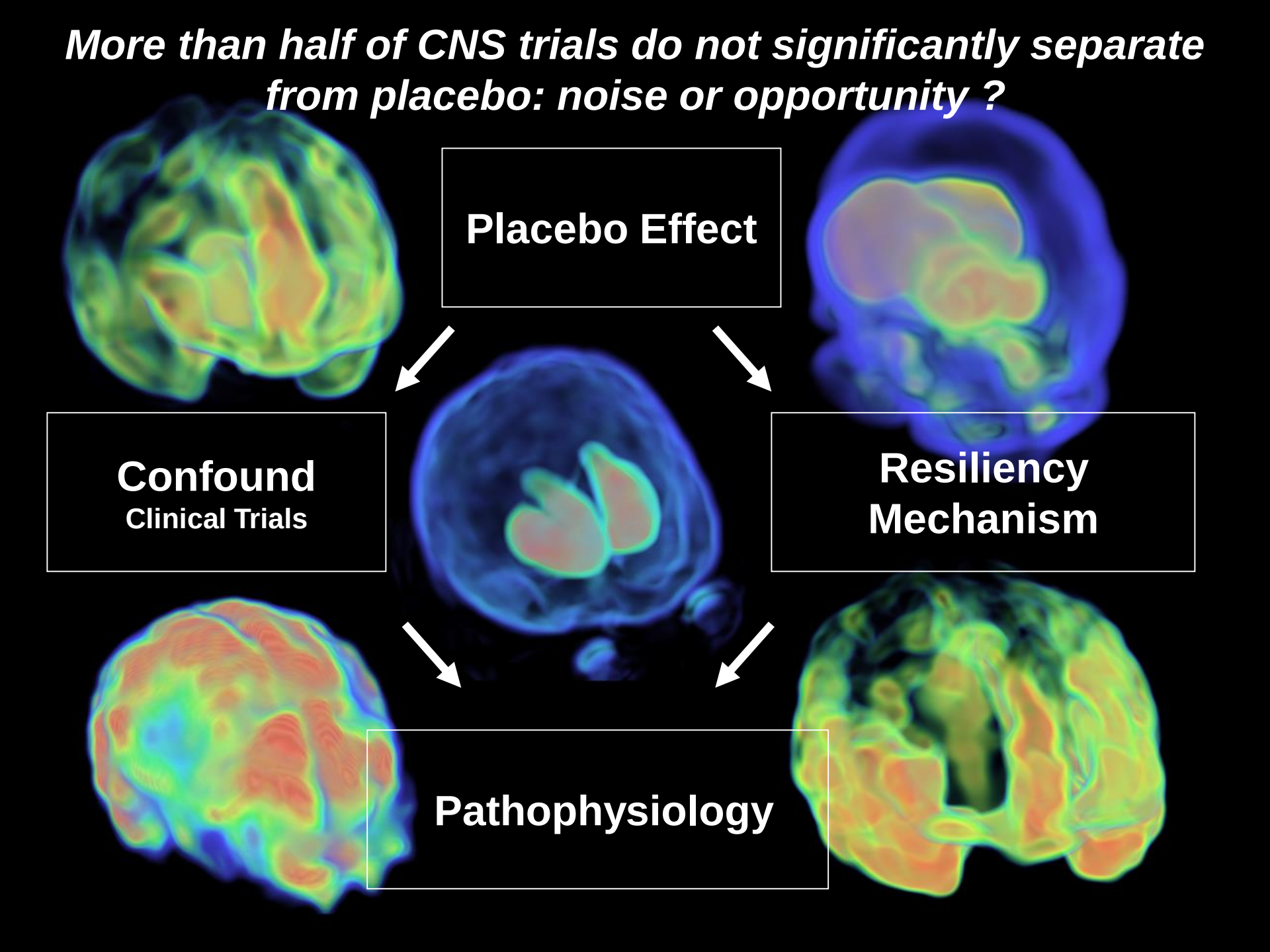
Run-in phase for screening centers based on band-pass filter



Why Placebo Responses in Clinical Trials?

- Spontaneous recovery (Natural History)
- Improvement in function while under observation (Hawthorne Effect)
- Response biases (wanting to please…)
- Use of subjective end points
- In clinical trials, a higher likelihood of receiving active treatment (greater levels of positive expectancy), higher frequency of appointments, greater rapport with clinician, same clinician, have been associated with lesser separation between placebo and active arms in randomized, controlled trials.

More than half of CNS trials do not significantly separate from placebo: noise or opportunity ?

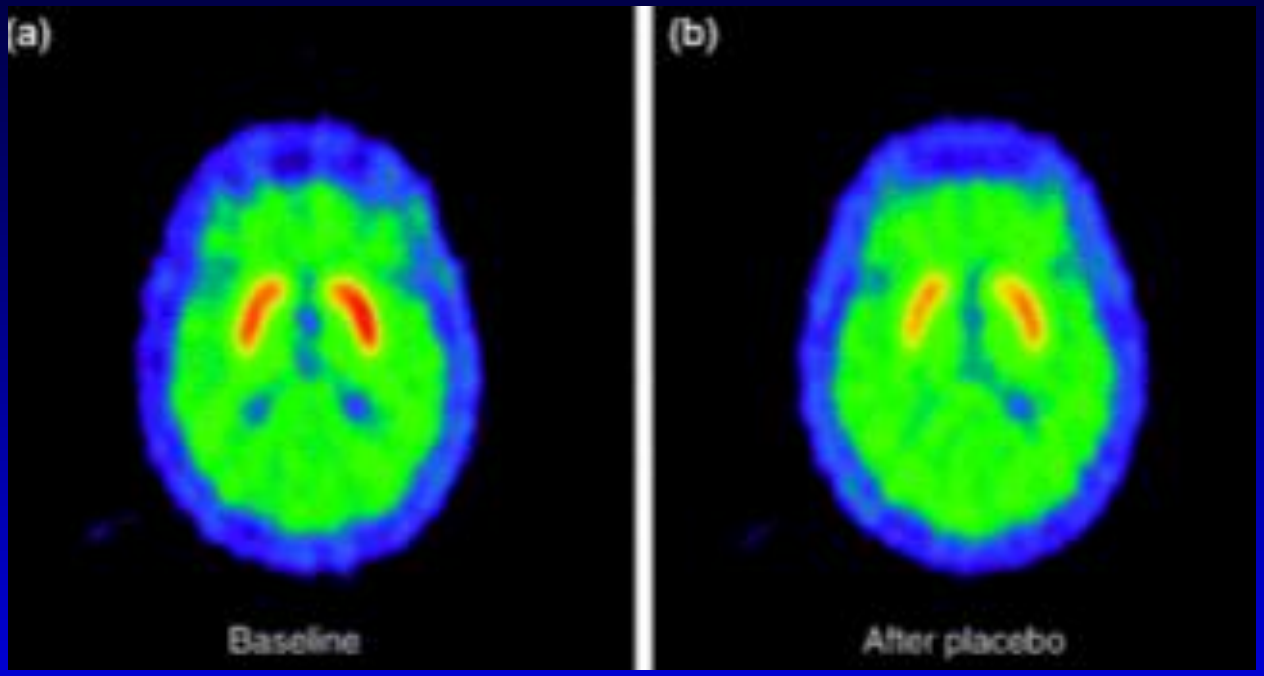


Background

It started with pain

- In post-surgical patients, or in experimental pain models (e.g., ischemic pain), expectation of analgesia during placebo administration was associated with reductions in pain ratings
- This effect was antagonized by naloxone, whether using open or hidden injections (Levine et al., 1978; Gracely et al., 1983; Grevert et al., 1983; Levine et al., 1984; Benedetti et al., 1984; Amanzio and Benedetti 1999)
- Using fMRI and phasic pain, placebo (topical cream) was associated with reductions in the activity of anterior cingulate, thalamus, insula. Anticipation of placebo associated with activation of DLPFC (Wager et al., 2004)
- Rostral anterior cingulate activation and its relationship with placebo effects has now been replicated across a number of studies using fMRI

Placebo Administration in Parkinson's Disease



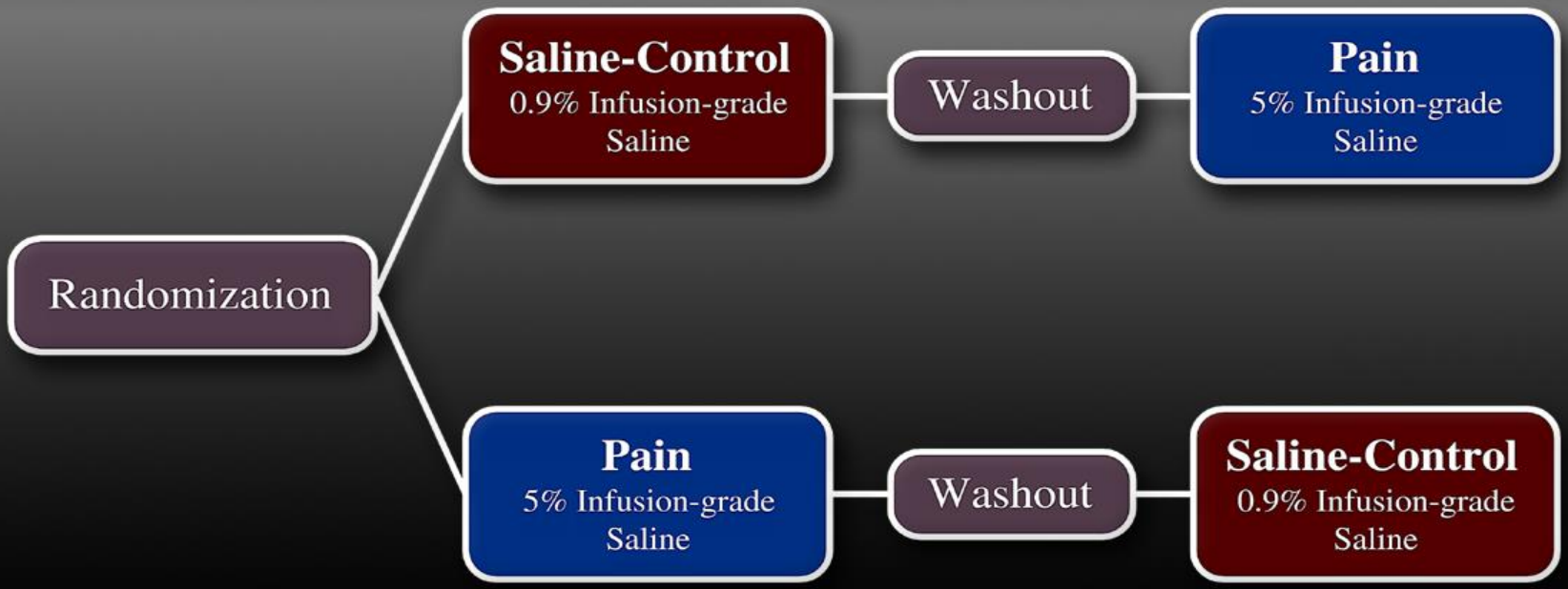
Placebo-induced changes in RAC binding potential in the striatum of patients with PD. Within-subject placebo-induced changes in RAC binding potential tended to be greater in the striatum contralateral to the more affected body side (20%) than in the ipsilateral striatum (17%).

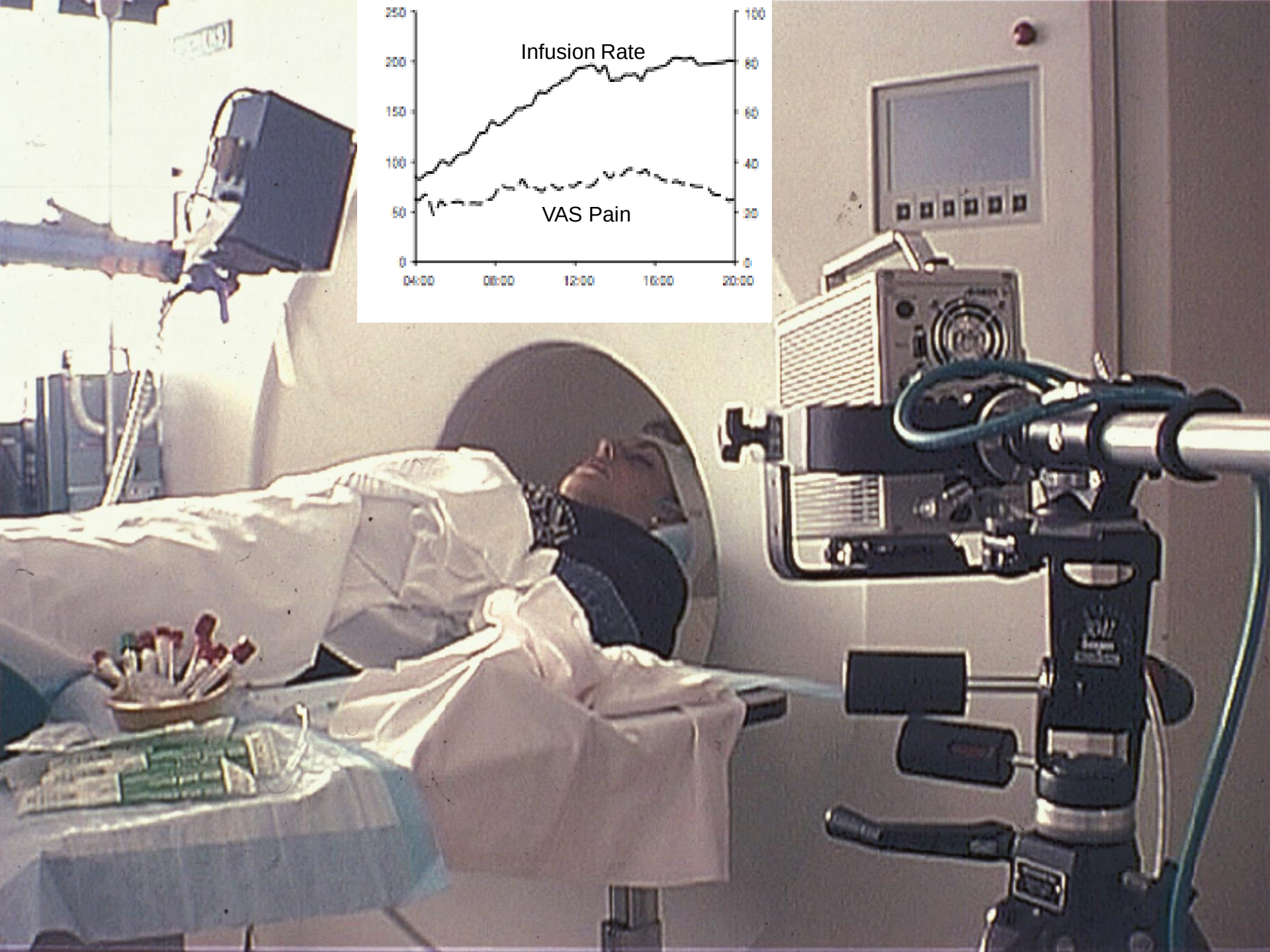
The placebo group and the open group did not differ in their baseline placebo-free RAC binding potential values

R. de la Fuente-Fernandez et al., Science 293, 1164 -1166 (2001)

Saline-Control

Pain

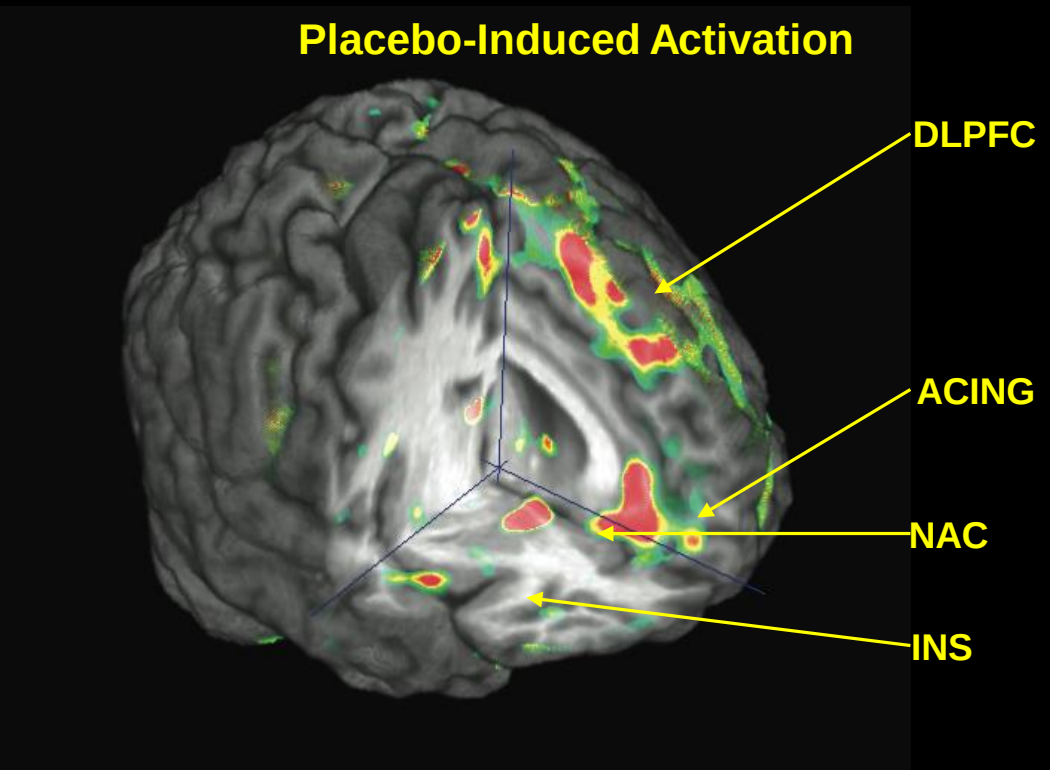


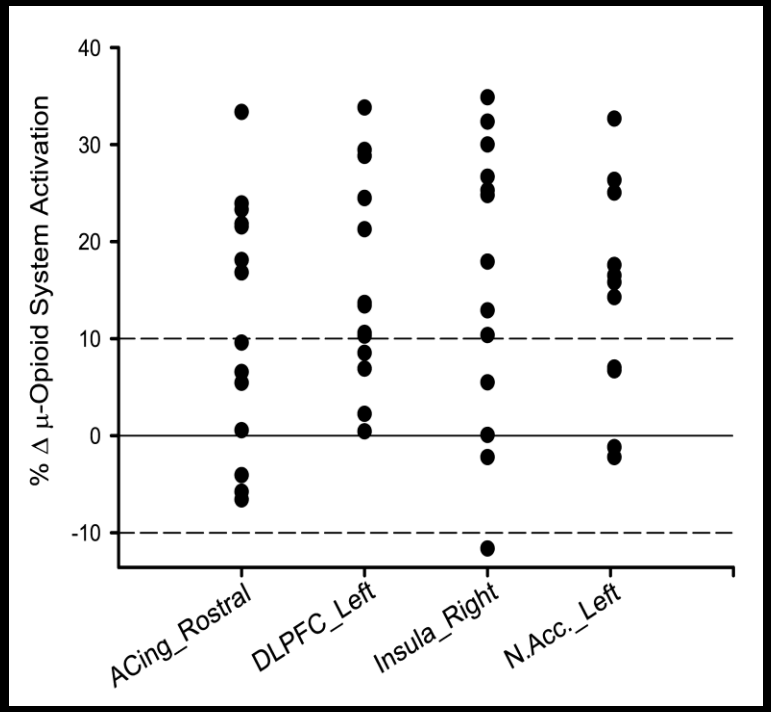

Infusion Rate
VAS Pain
250
200
150
100
50
0
100
80
60
40
20
0
04:00
08:00
12:00
16:00
20:00

Effects of Placebo Administration

Standard Clinical Trial Instructions
"This agent may be either an inert substance or a compound that enhances the body's ability to counter pain"

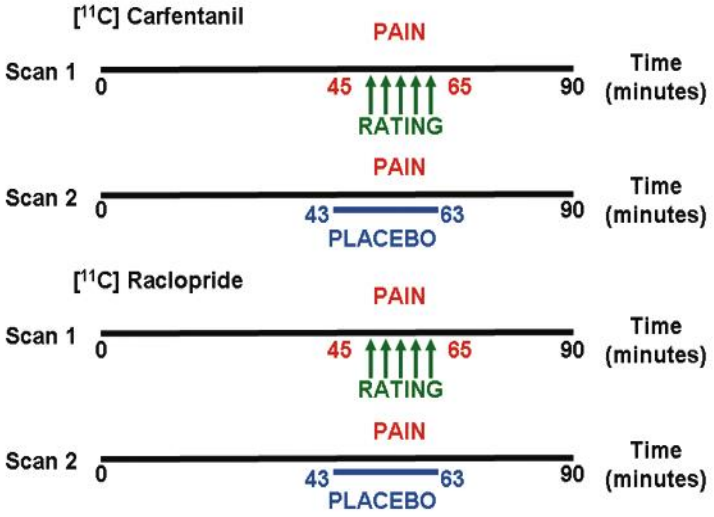
Placebo introduced every 4 min intravenously (1 ml, 0.9% saline *i.v.*).





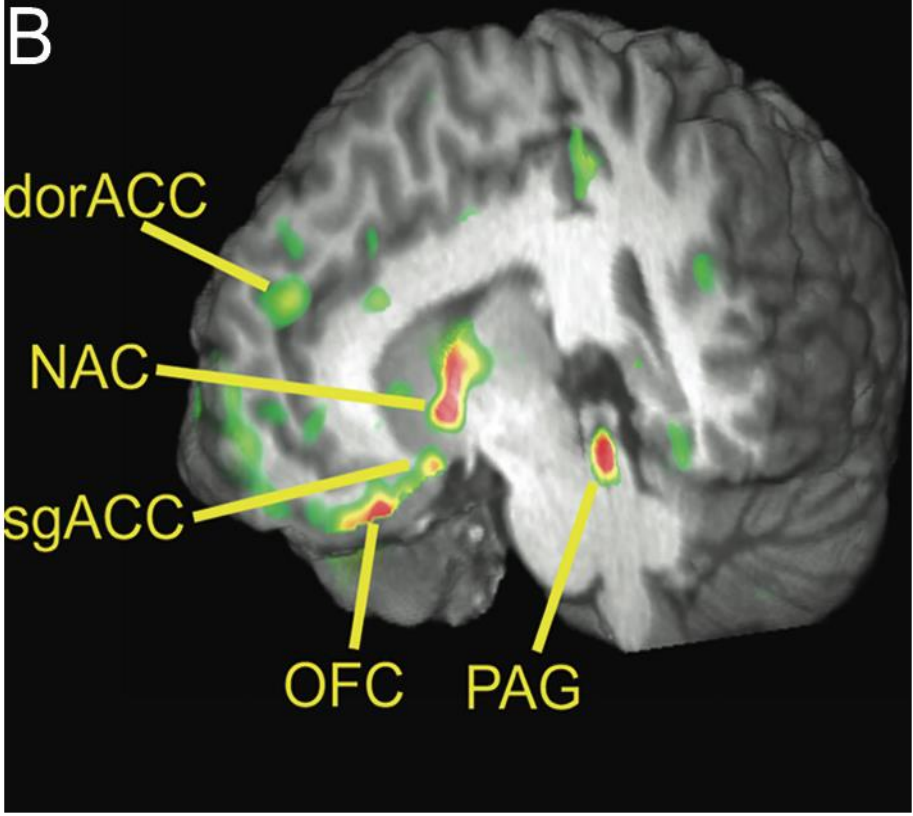
(Zubieta et al., J Neuroscience 25:7754, 2005)

A

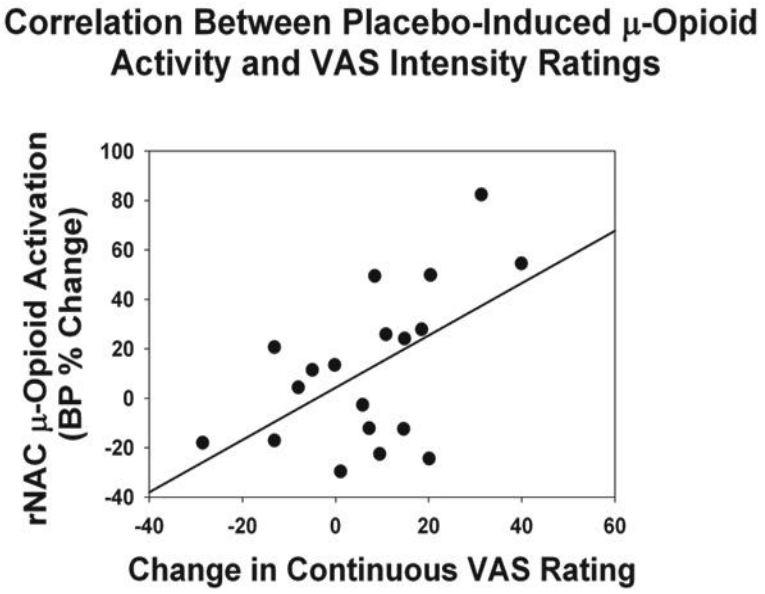


(Scott et al.,Arch Gen Psychiatry, 2008)

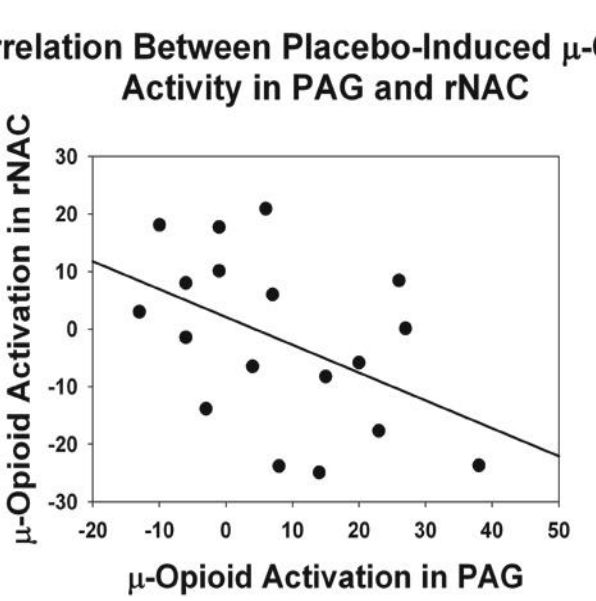
B



C

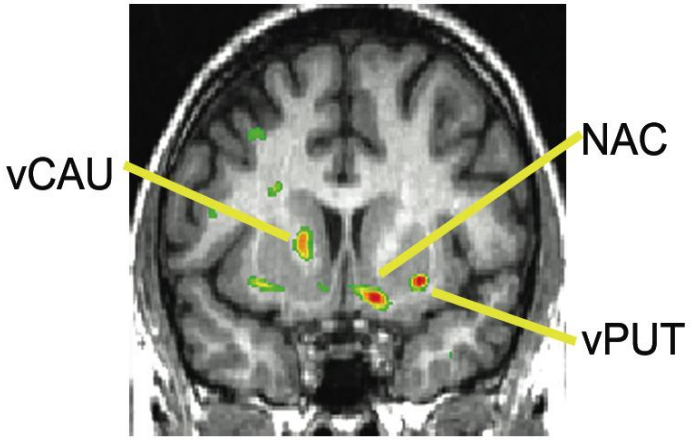


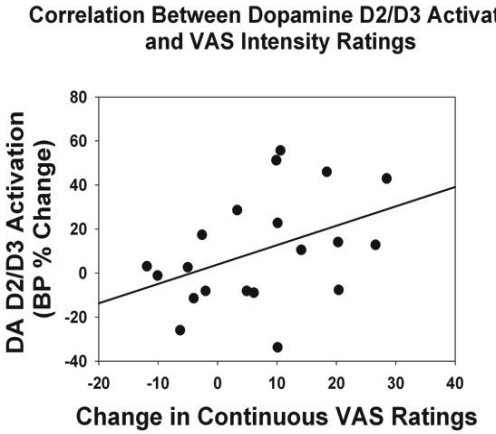
D



A

Placebo-Induced Activation of Dopamine D2/D3 Neurotransmission

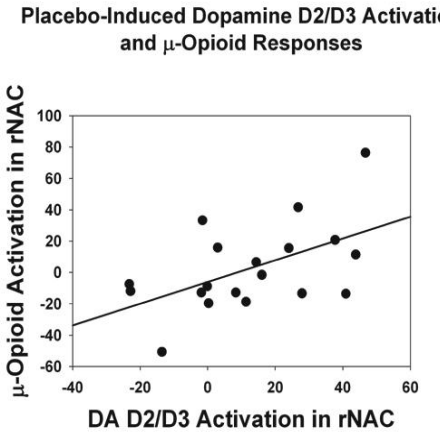


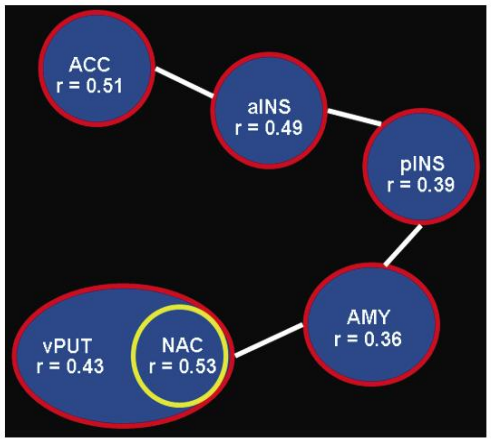


Placebo-induced nucleus accumbens dopamine release during pain accounted for 25% of the variance in the formation of placebo analgesic effects

B

Correlations Between NAC Dopamine D2/D3 Activation and μ-Opioid Responses



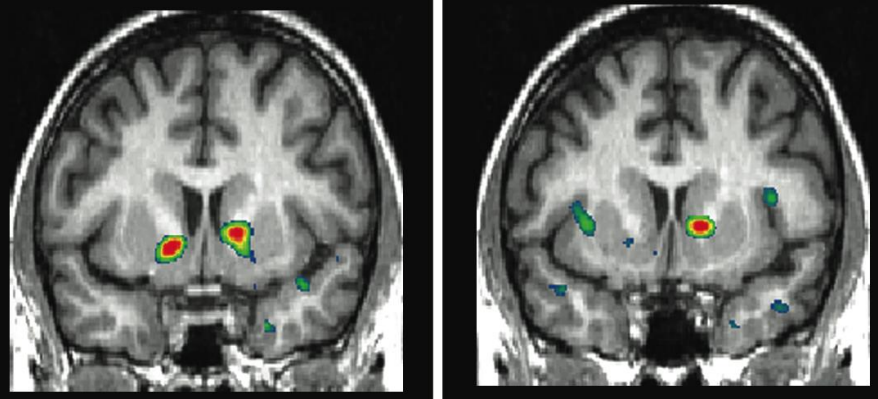


(Scott et al.,Arch Gen Psychiatry, 2008)

There is a neurobiology to it: Opposite Responses of Opioid and Dopamine Circuits Underlie Placebo and Nocebo Effects

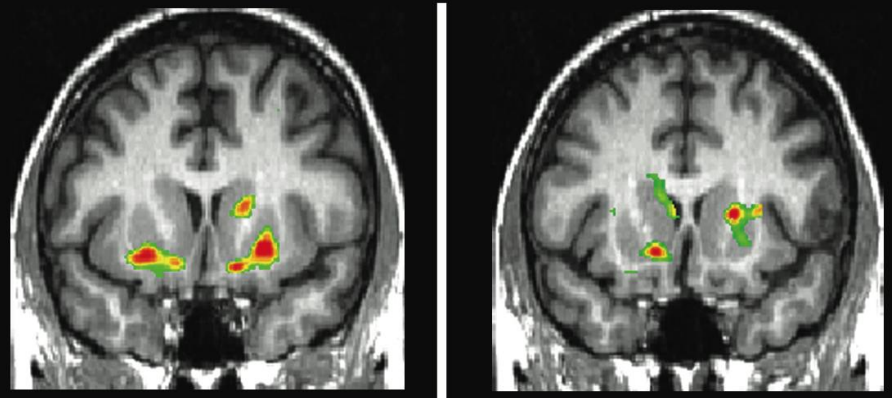
Responders vs. Non-Responders | Placebo vs. Nocebo Responders

μ-OPIOID

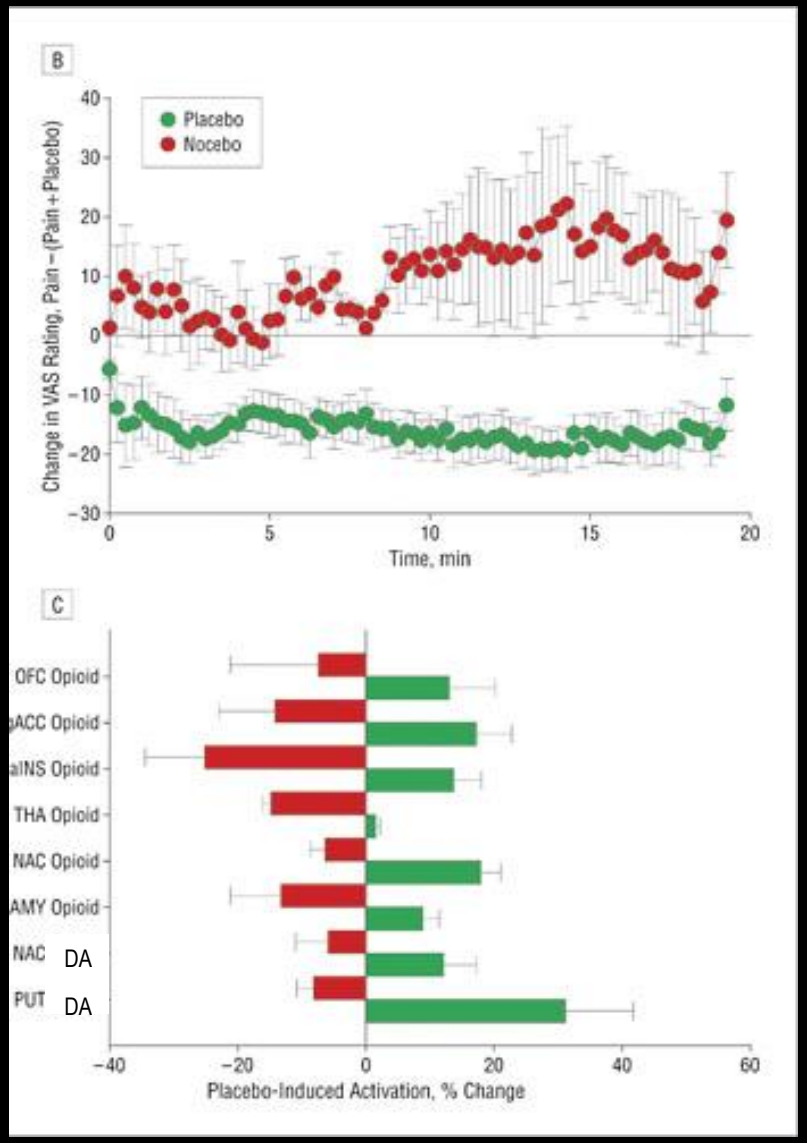


Z scores
4
3
2
1

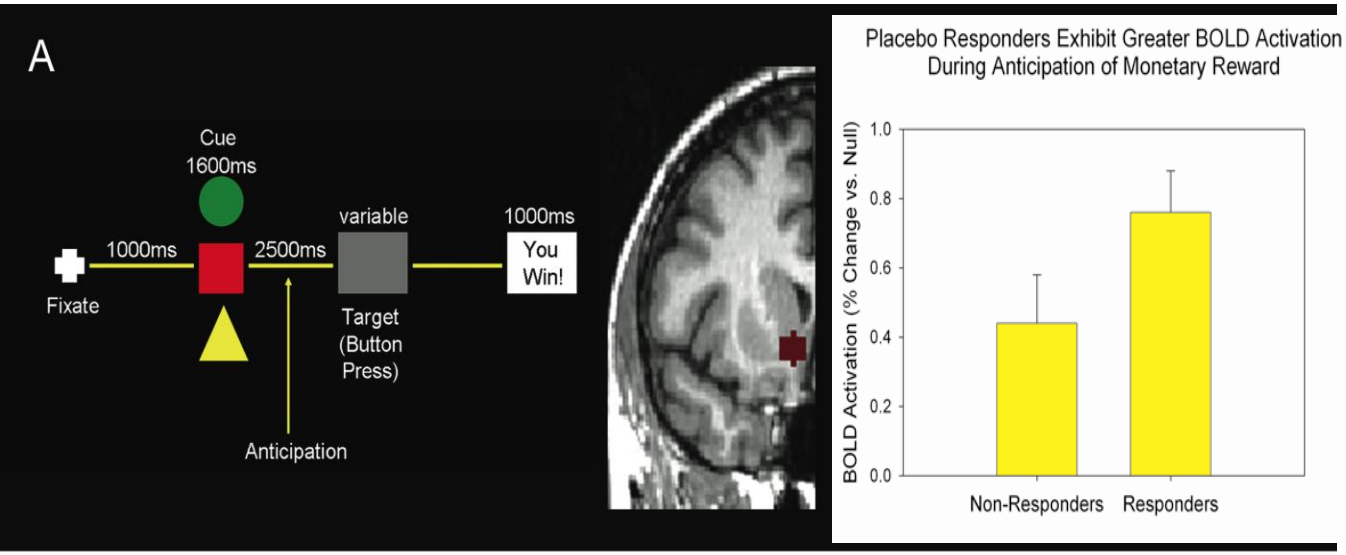
DOPAMINE D2/D3

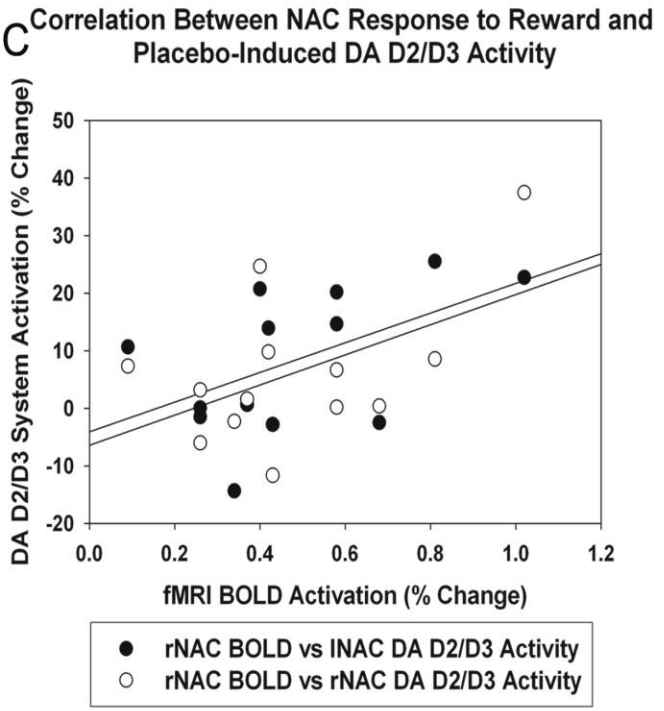


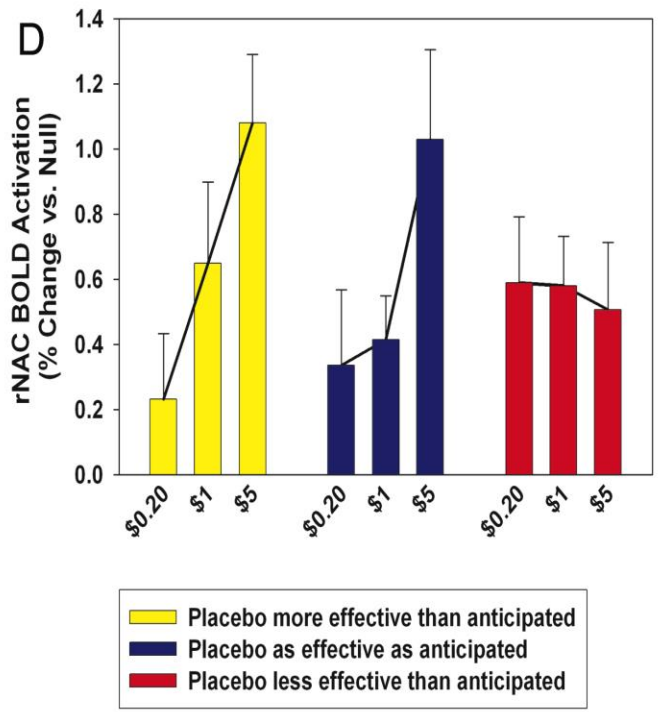
Scott et al., Arch Gen Psychiatry, 2008



Intrinsic differences in the response of reward anticipation circuits in placebo non-responders: PET + fMRI analysis



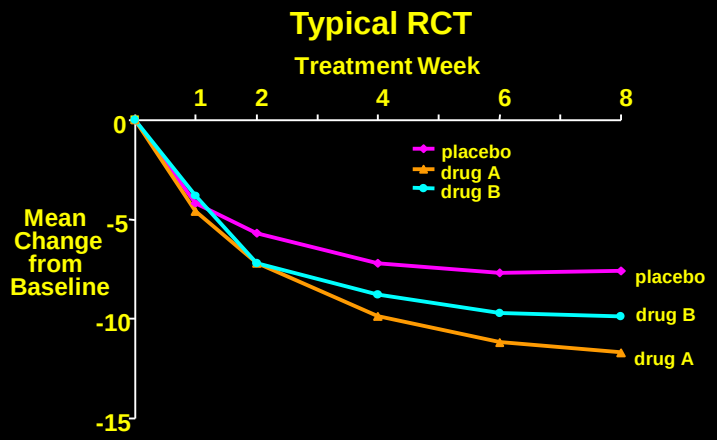




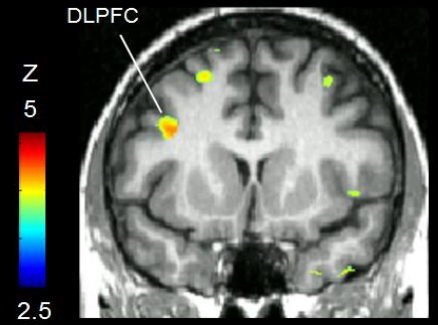
Nucleus accumbens activity during reward expectation responding predicted 28% of the variance in the formation of placebo analgesic effects

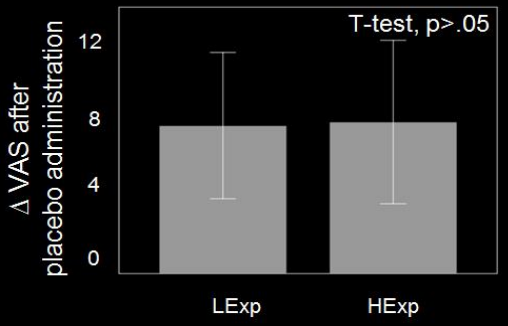
(Scott et al.,Neuron, 2007)

Placebo Effect: Reward Expectations or Error Detection?

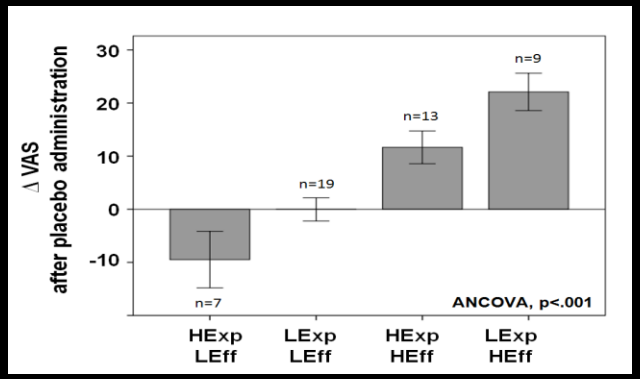


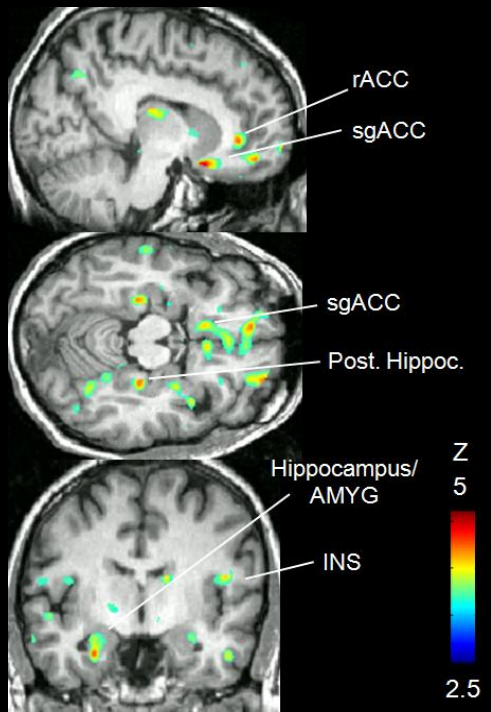
Effect of Expectations

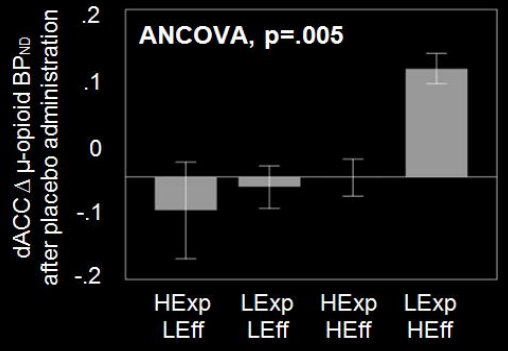


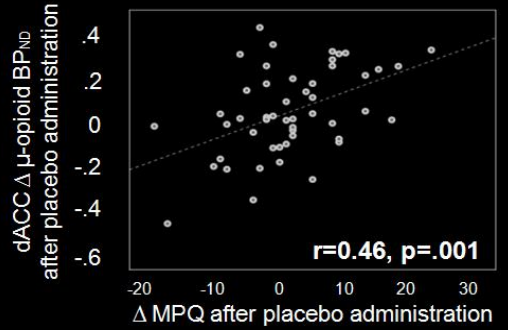


Effect of Expectations – Subjective Effectiveness





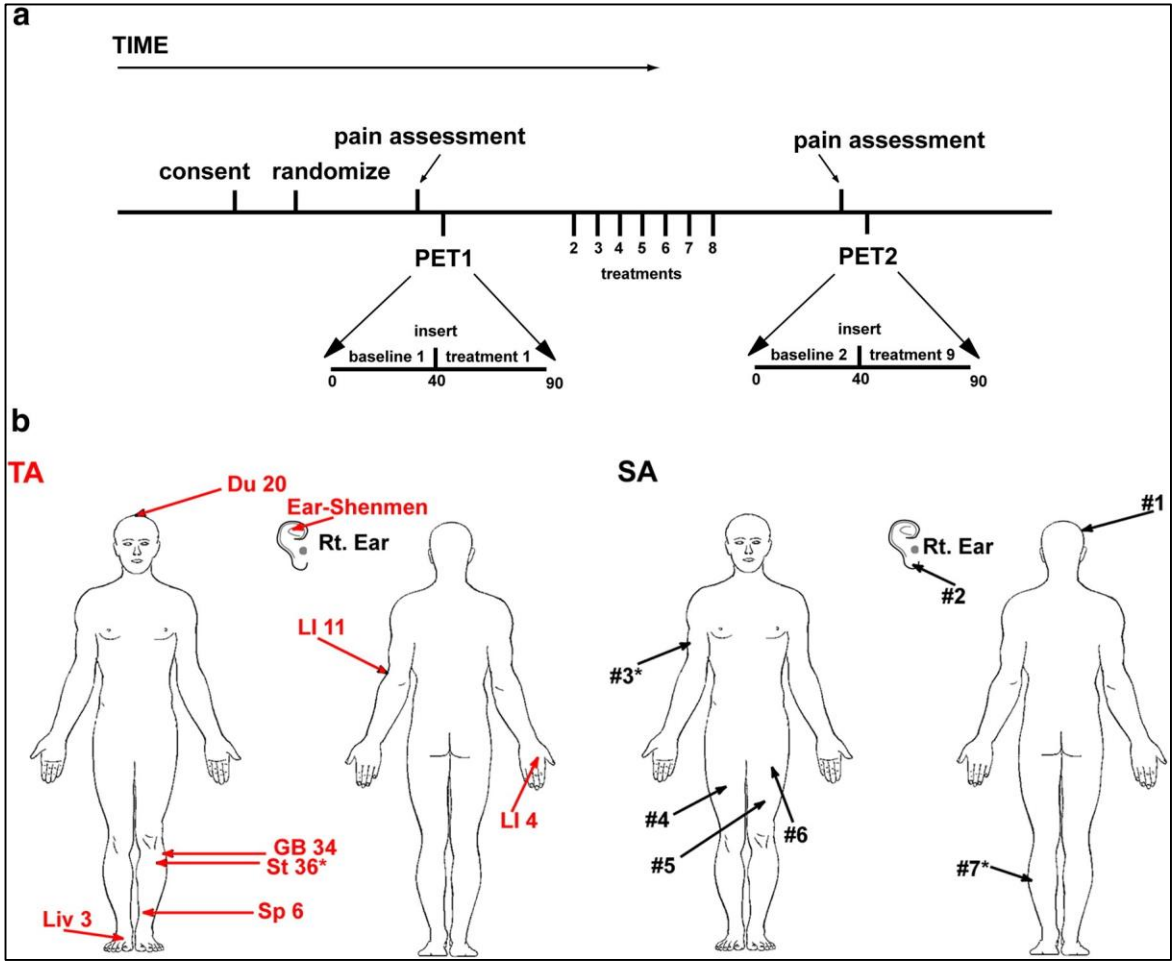


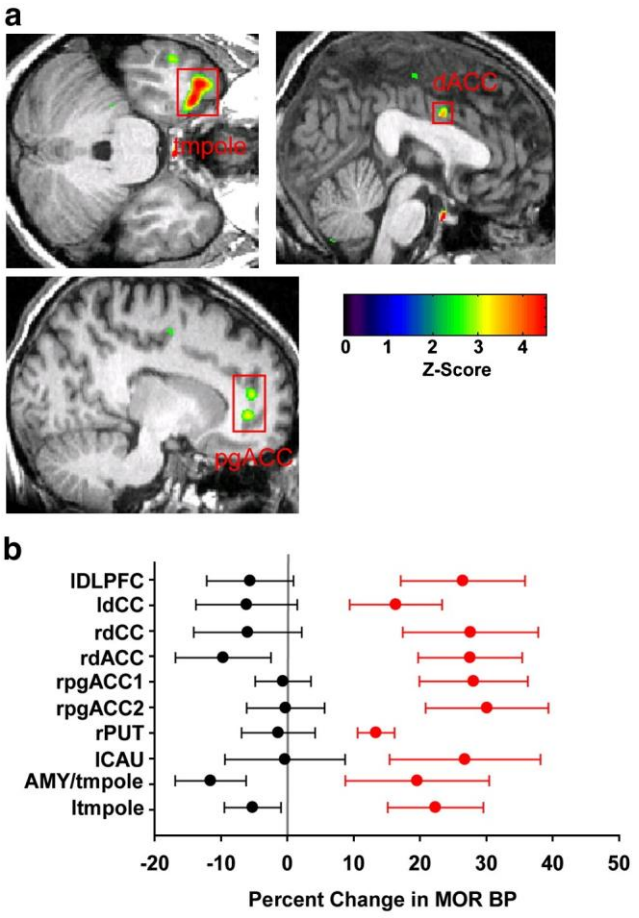


Peciña et al., Soc Cog Affect Neurosci, 2013

Utility of Biomarkers in Clinical Trials

Effects of Verum and Sham Acupuncture in Fibromyalgia





(Harris et al., 2009)

Predicting Placebo Responses: Trait Effects

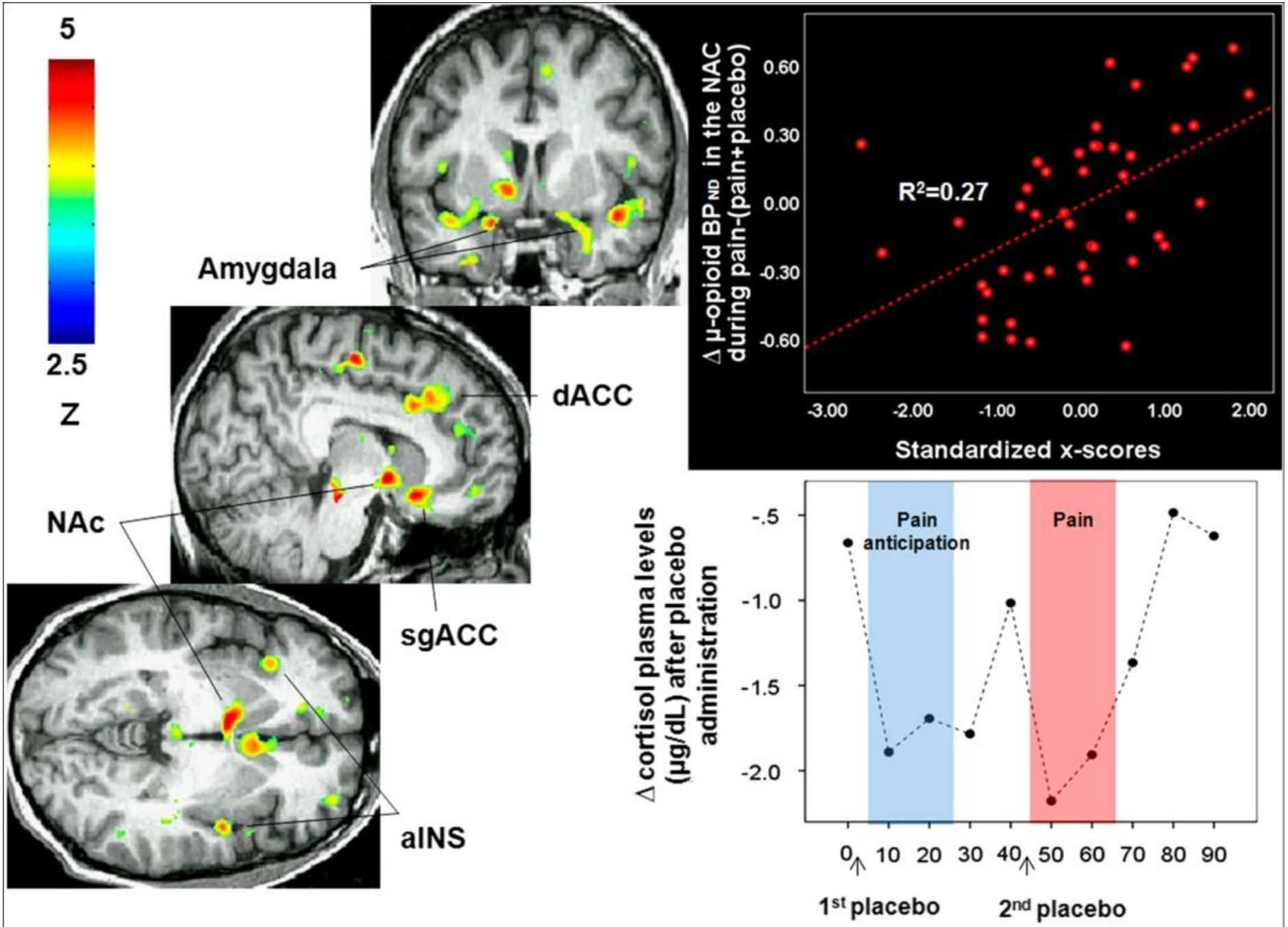
- **15 trait variables were selected from various instruments: ER89, NEO-PI, BIS/BAS, LOT-R, WB, STAI**

- **3 variables, ER89 (ego resiliency) and NEO-PI Agreeableness and Neuroticism explained 28% of the variance in placebo analgesia**

- **Decomposed the NEO facets Agreeableness and Neuroticism into their 12 subscales and data reduced:**
  4 scales (3 positive predictors, ER89, NEO altruism, NEO straightforwardness; 1 negative predictors, NEO angry-hostility), explained 25% of the variance in placebo analgesic effects

- **These variables were associated with placebo-induced endogenous opioid system activation and cortisol suppression**

(Peciña et al., Neuropsychopharmacology, 2013)



Molecular Psychiatry

Genetic Variation

Marta Peciña

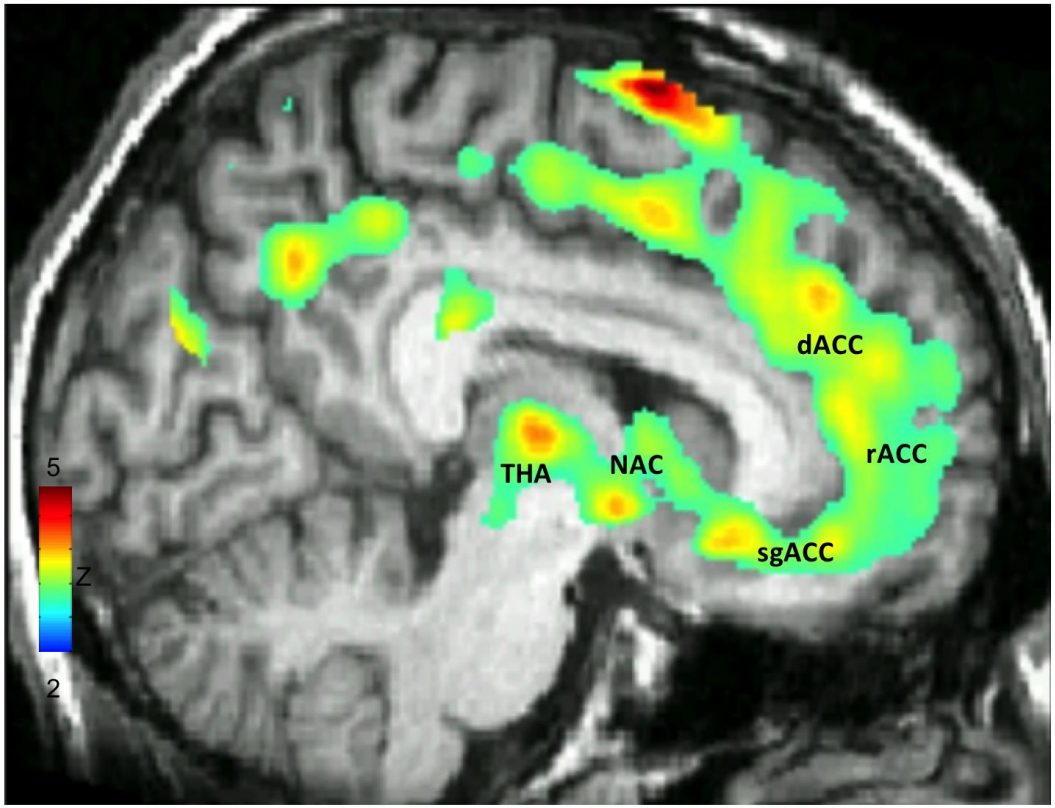
MOR $A^{118}G$

COMT $val^{158}met$

BDNF $val^{66}met$

FAAH C ^{385} A

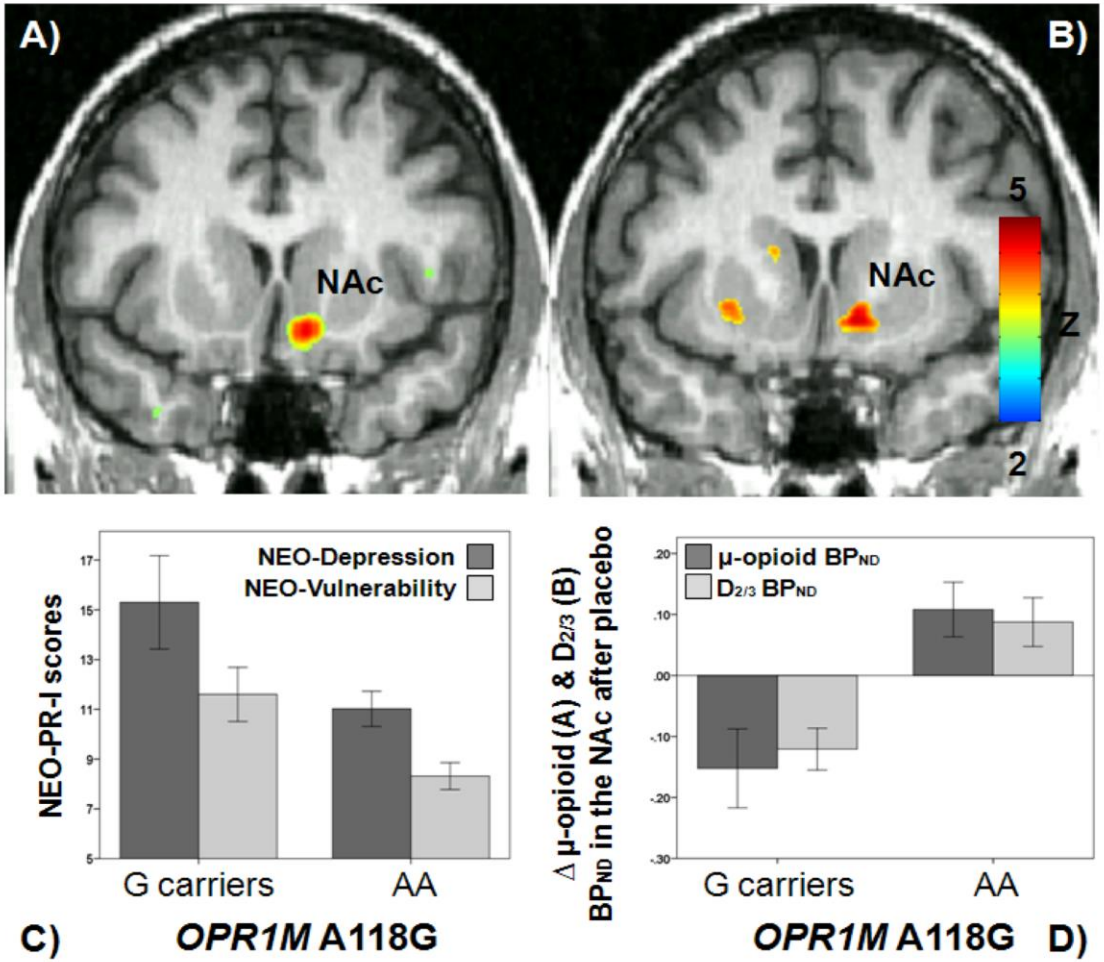
***OPRM1* A118G effect on μ-opioid receptor availability at baseline (AA>G carriers).** AA homozygotes, compared to G carriers, showed greater μ-opioid receptor binding in regions that included the anterior cingulate cortex (subgenual, rostral and dorsal ACC), the ventral striatum (NAC) and the thalamus (THA) among others.



Peciña et al., Neuropsychopharmacol (2014)

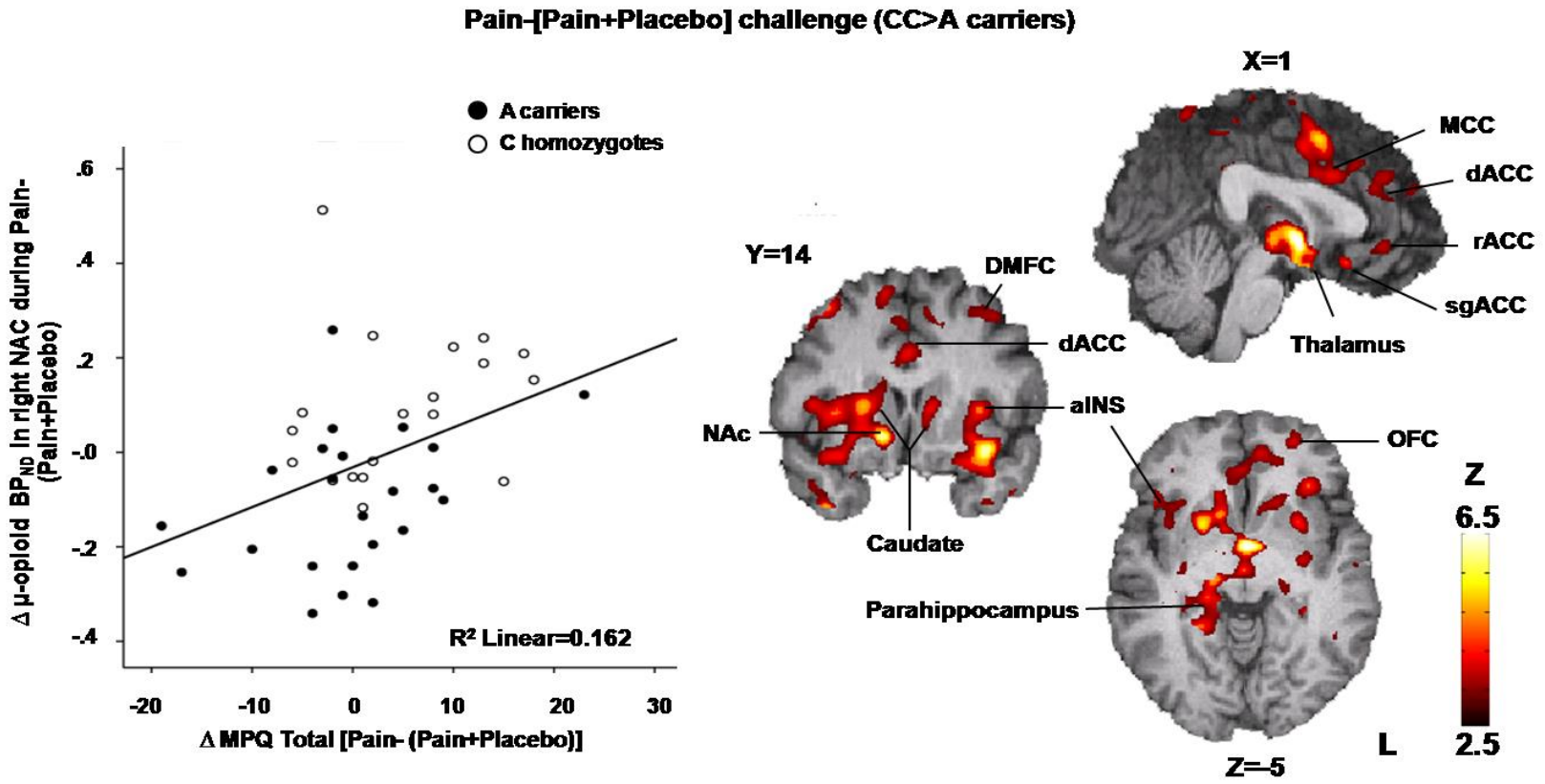
OPRM1 A118G effect on changes in μ-opioid and $D_{2/3}$ activation during placebo

AA homozygotes, compared to G carriers, showed greater placebo induced μ-opioid (A, D) and $D_{2/3}$ (B, D) activation systems in the NAc after placebo. AA homozygotes showed lower scores in the NEO-Depression and NEO-Vulnerability facets of the NEO-Neuroticism domain (C).



Peciña et al., Neuropsychopharmacol (2014)

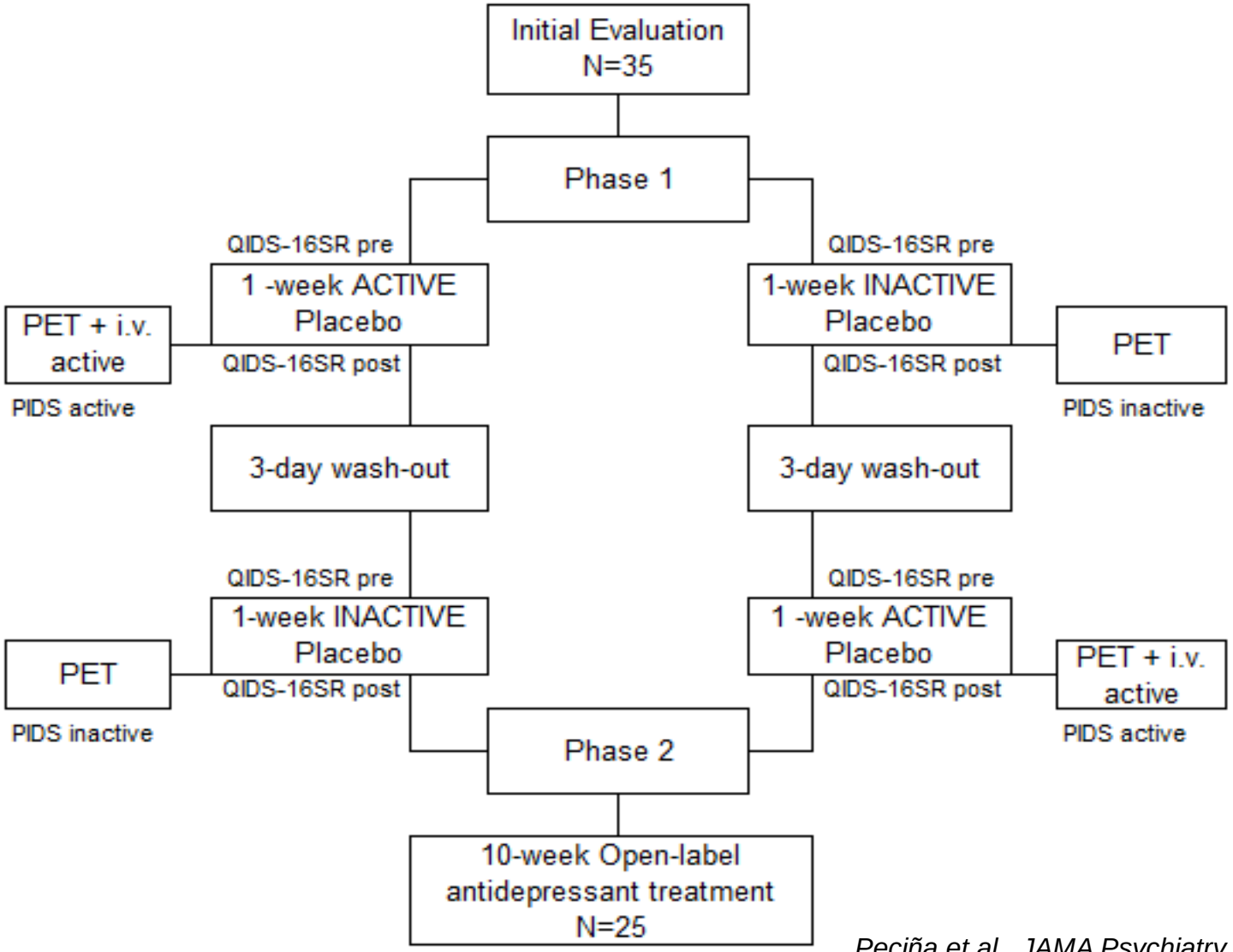
FAAH C385A polymorphism (Pro129Thr missense variant)



- **Selective Effect on Opioid Neurotransmission, not on Dopamine**
- **Associated with Greater Placebo Analgesia and Placebo-Induced Positive Affective State**
- **No Effects on Pain Psychophysics**

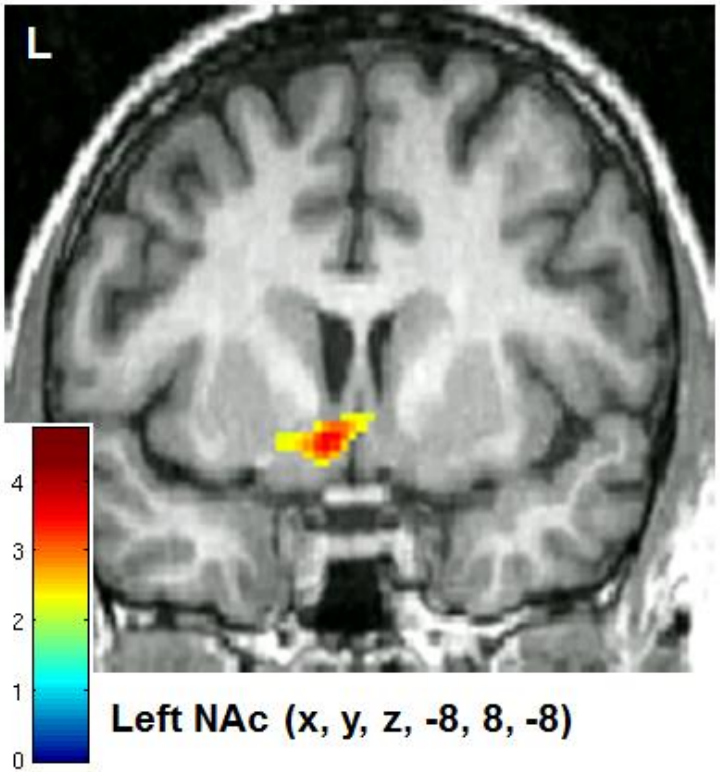
Peciña et al., Molecular Psychiatry, 2014

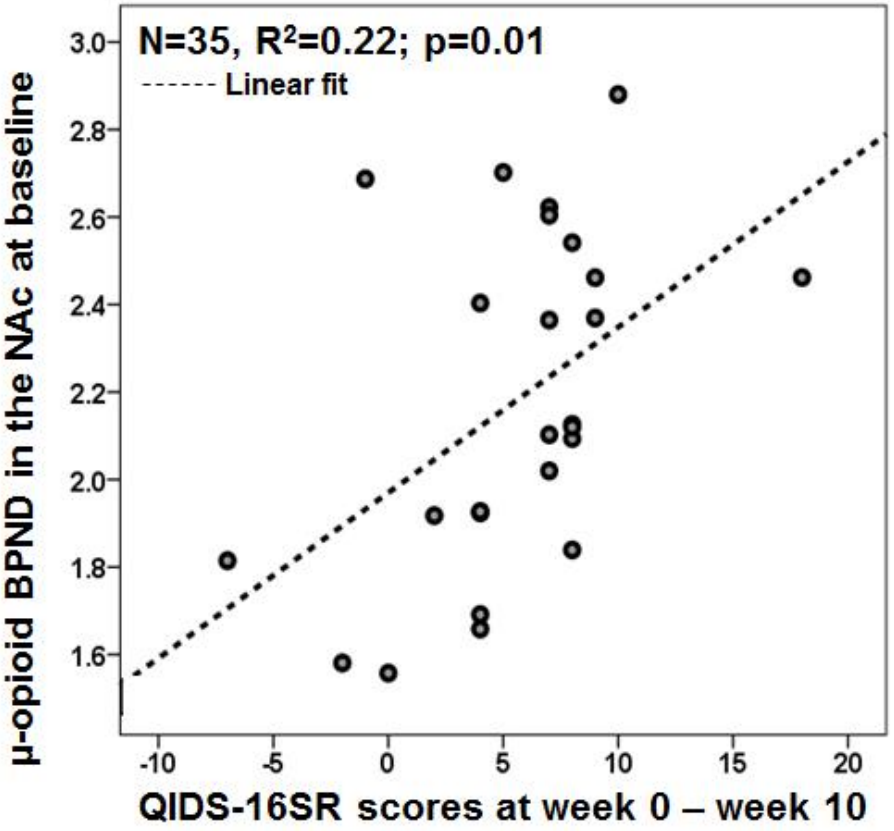
Are these mechanisms generalizable? A study in Major Depression



Peciña et al., JAMA Psychiatry (2015)

Baseline μ-opioid receptor BP_{ND}



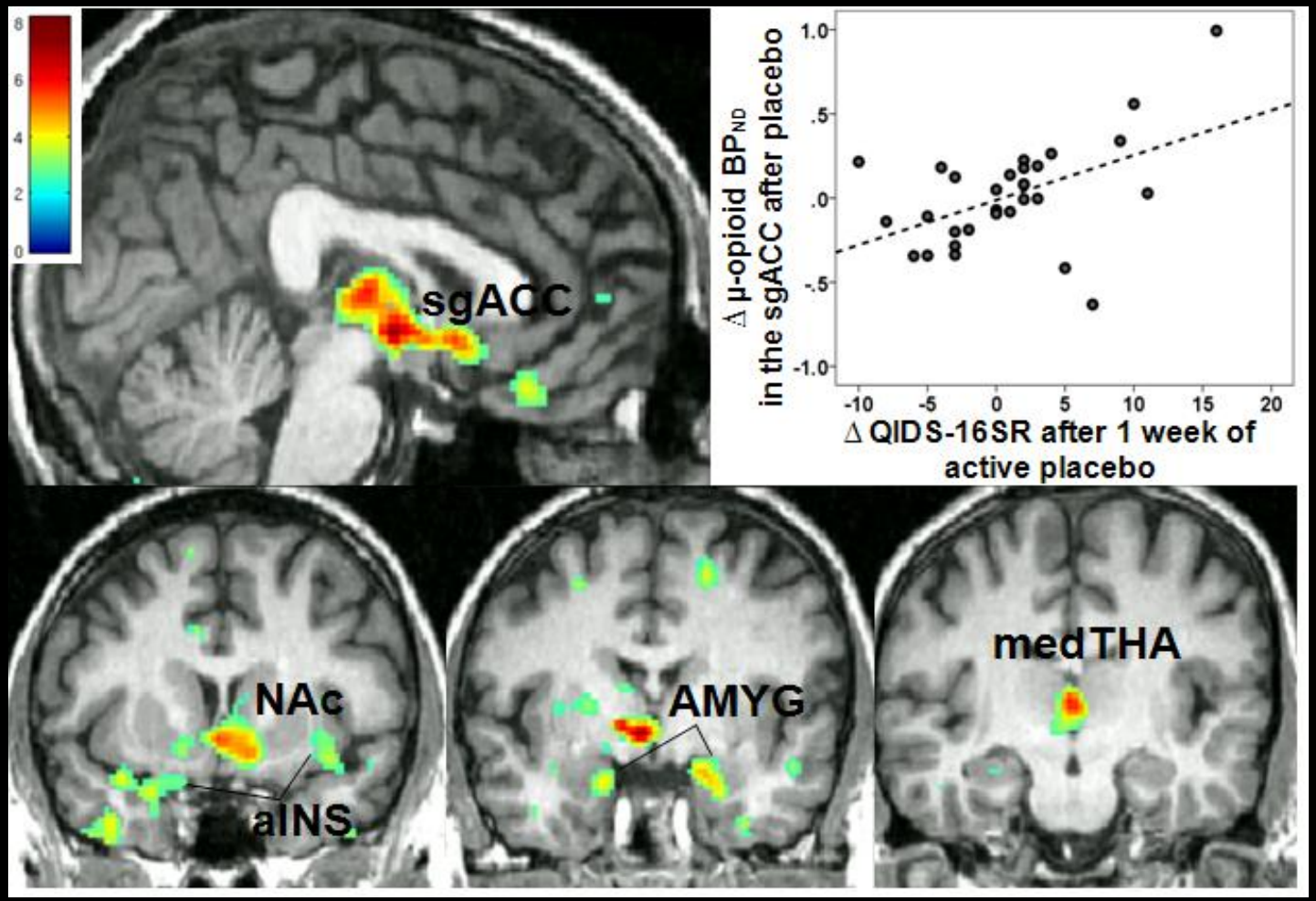


Positive correlation with symptom severity

Positive correlation with response to SSRI

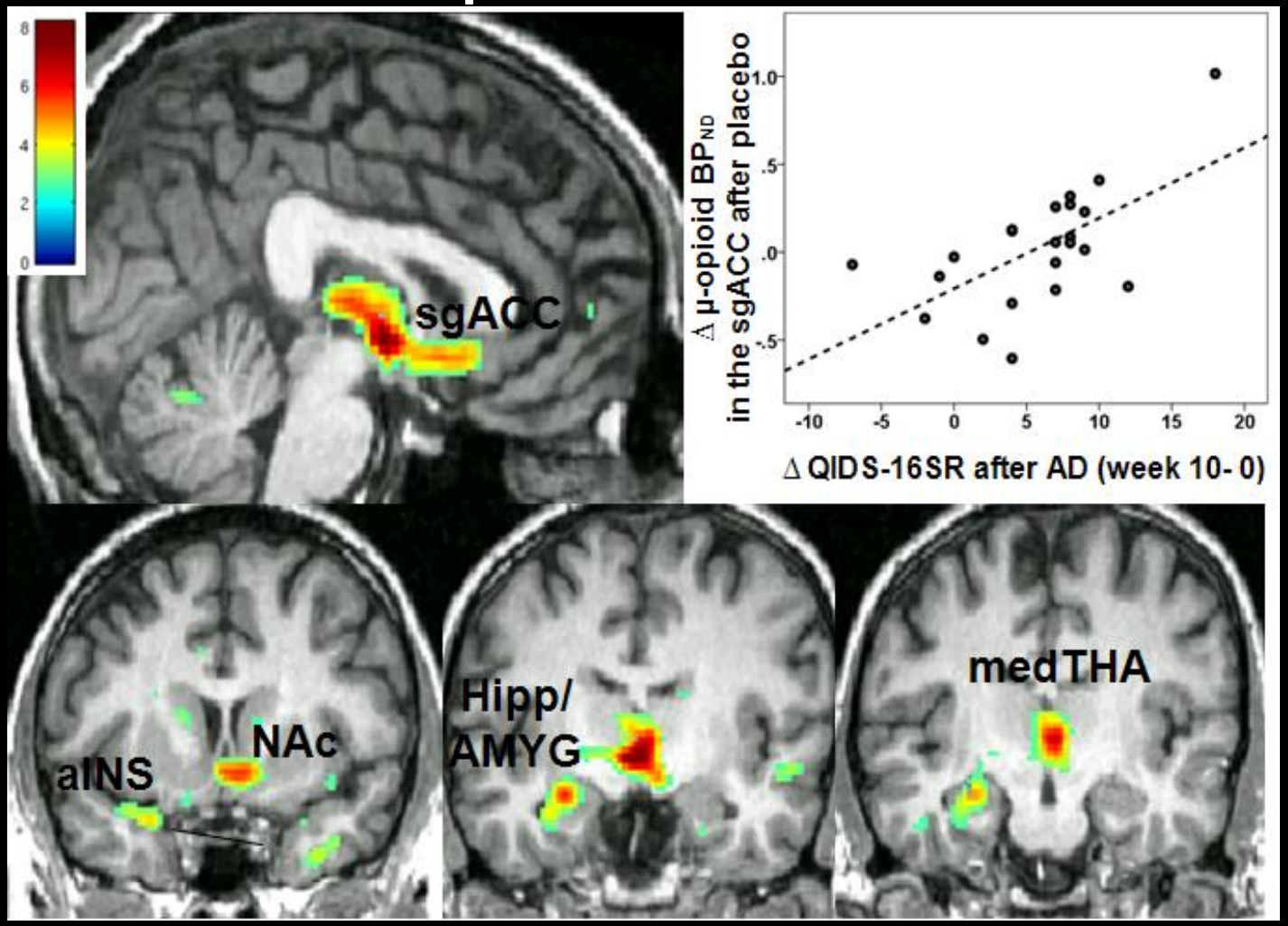
Peciña et al., JAMA Psychiatry (2015)

Voxel by voxel correlational analysis between Δ in μ-opioid BP_{ND} and Δ in QIDS-16SR after 1 week of placebo



Peciña et al., JAMA Psychiatry (2015)

Voxel by voxel correlational analysis between Δ in μ-opioid BP_{ND} and Δ in QIDS-16SR after 10 weeks of antidepressant treatment

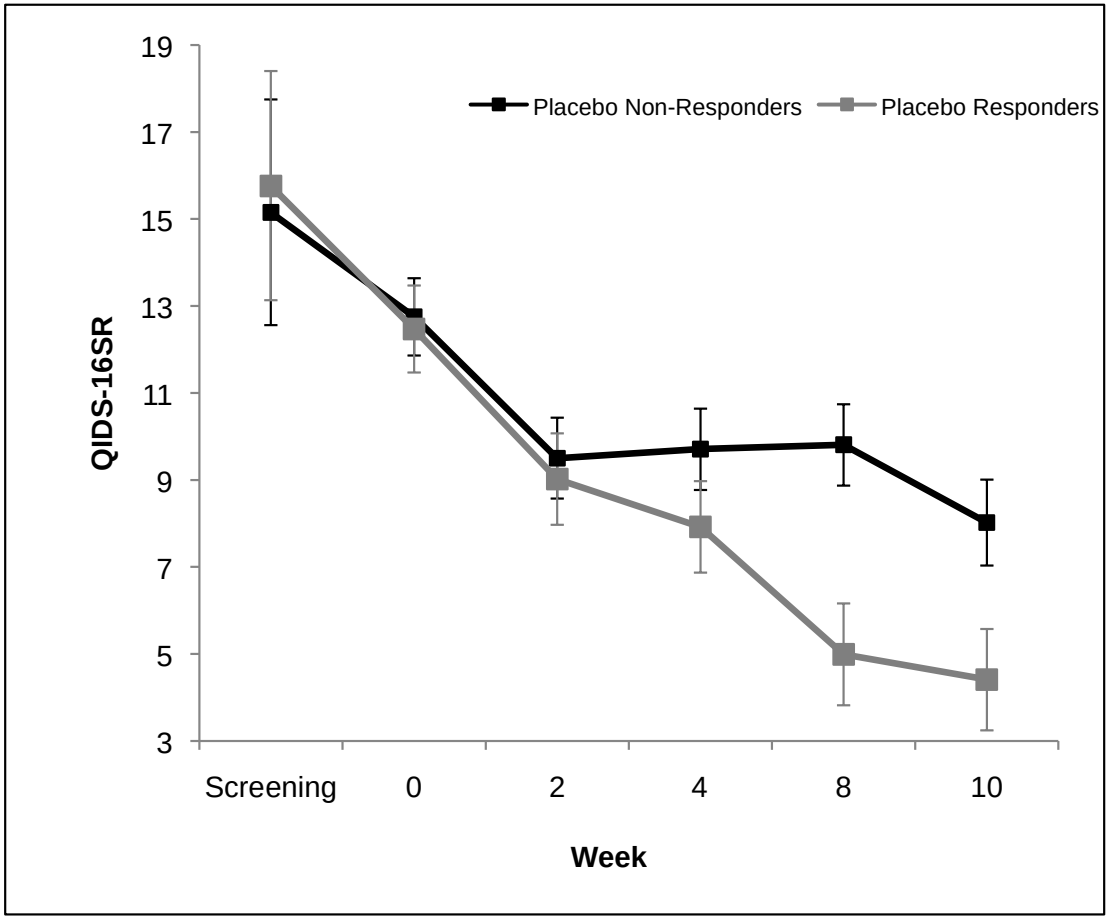


Peciña et al., JAMA Psychiatry (2015)

Clinical Consequences?

QIDS-16SR score by placebo group (responders versus non responders) over 10 weeks of antidepressant treatment

Overall remission rates (QIDS-RS_{16} ≤ 5) were higher in the placebo responder group versus non-responders (χ^2=6.1, p=0.03), and placebo responders showed greater improvement in depression symptoms over the 10-week antidepressant trial (N=29)



Peciña et al., 2015

Conclusions

- **Both opioid and dopaminergic systems appear involved in the formation of placebo responses, potentially across pathologies (e.g., Pain, Parkinson disease, MDD).**

- **Interindividual variation in placebo responses, some of which can be traced to common genetic polymorphisms and simple trait measures, is relevant not only for clinical trials, but also the understanding of mechanisms related to vulnerability and resiliency to disease, including treatment responses.**

Questions?

- Does an integrity of stress regulatory mechanisms influence responses to antidepressant treatments?
- What is the interaction between placebo-responsive mechanisms and antidepressant effects?
- Would placebo responses imply a greater response to non-interventional approaches (e.g., therapies)?
- Would biomarkers linked to, for example, the response of the endogenous opioid system, allow stratification in clinical trials?

The Team …

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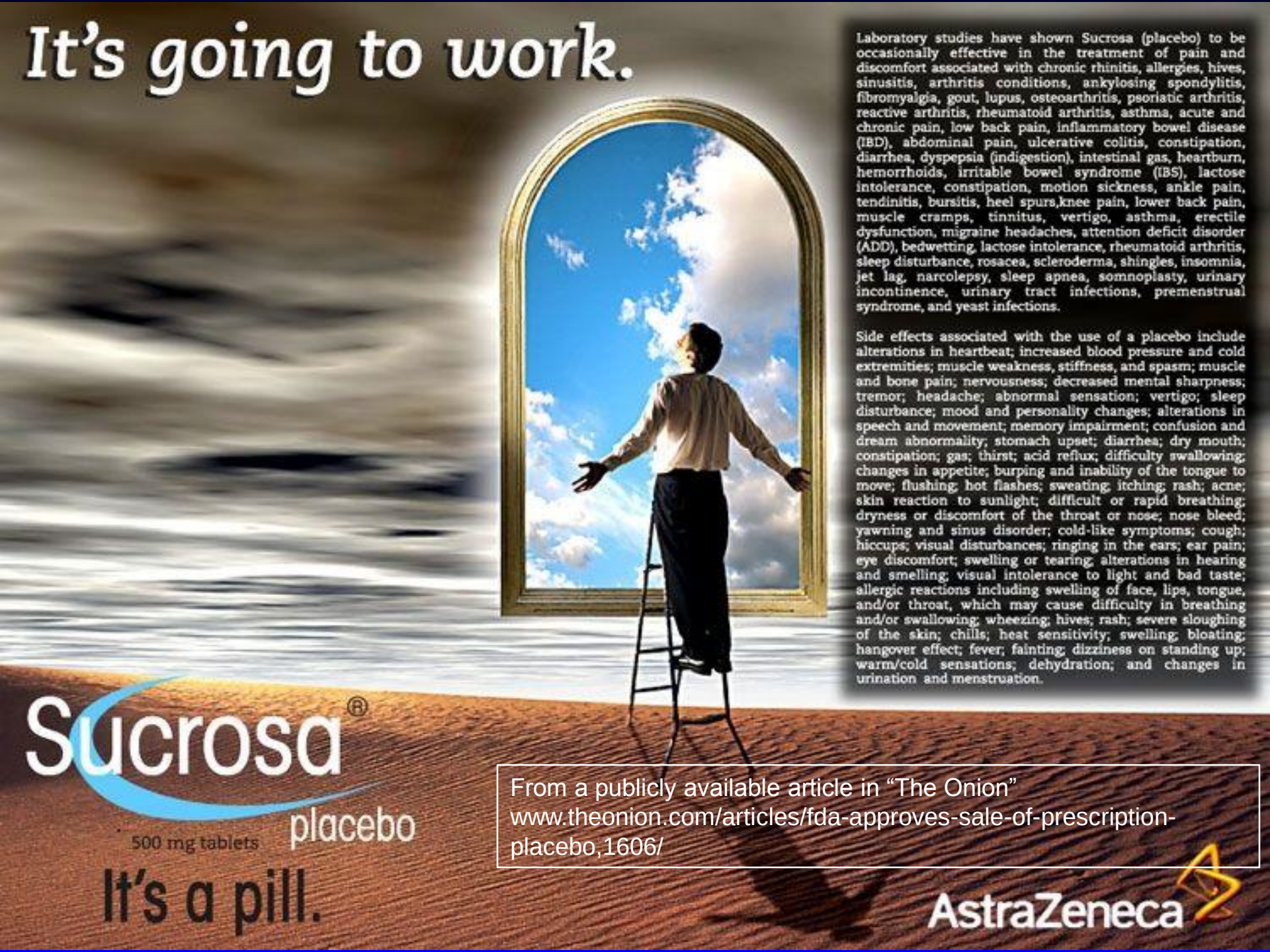

From a publicly available article in "The Onion"
www.theonion.com/articles/fda-approves-sale-of-prescription-placebo,1606/